IN THE UNITED STATES DISTRICT COURT

IN AND FOR THE DISTRICT OF DELAWARE

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SHIRE DEVELOPMENT INC., SHIRE PHARMACEUTICAL DEVELOPMENT, INC., COSMO TECHNOLOGIES LIMITED, and GIULIANI INTERNATIONAL LIMITED,	:	CIVIL ACTION
Plaintiffs,	:	
v	:	
CADILA HEALTHCARE LIMITED (d/b/a ZYDUS CADIL) and ZYDUS PHARMACEUTICALS (USA) INC.,	:	
Defendants.	:	NO. 10-581-KAJ

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Wilmington, Delaware
Tuesday, March 29, 2016
Bench Trial - Volume B

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BEFORE: HONORABLE **KENT A. JORDAN**, U.S.C.C.J.

APPEARANCES:

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RICHARDS, LAYTON & FINGER, P.A.
BY: FREDERICK L. COTTRELL, III, ESQ.,
KELLY E. FARNAN, ESQ., and
JASON J. RAWNSLEY, ESQ.

-and-

FROMMER LAWRENCE & HAUG, LLP
BY: EDGAR H. HAUG, ESQ.,
ANGUS CHEN, ESQ.,
JASON A. LIEF, ESQ.,
DAVID A. ZWALLY, ESQ.
ANDREW WASSON, and
ELIZABETH MURPHY, ESQ.
(New York, New York)

Counsel on behalf of Plaintiffs

APPEARANCES: (Continued)

PHILLIPS, GOLDMAN, McLAUGHLIN & HALL, P.A.
BY: JOHN C. PHILLIPS, JR., ESQ., and
DAVID A. BILSON, ESQ.

-and-

LOCKE LORD, LLP
BY: MICHAEL J. GAERTNER, ESQ.,
KEITH D. PARR, P.C.,
JAMES T. PETERKA, ESQ.,
DAVID B. ABRAMOWITZ, ESQ.,
ANDY J. MILLER, ESQ.,
WASIM K. BLEIBEL, ESQ., and
TIMOTHY F. PETERSON, ESQ.
(Chicago, Illinois)

-and-

LOCKE LORD, LLP
BY: ANDREA L. WAYDA, ESQ.
(New York, New York)

Counsel on behalf of Defendants

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P R O C E E D I N G S

(REPORTER'S NOTE: The following bench trial was held in open court, beginning at 9:02 a.m.)

THE COURT: Good morning. Please be seated.

(The attorneys respond, "Good morning, Your Honor.")

THE COURT: Okay. A couple of logistic things real quick. I hope people will not mind indulging me this afternoon. I need to be off the bench by 12:15 and take a little bit longer for lunch than I ordinarily would, so perhaps I ought to take care of some other responsibilities. So if we can take off at 12:15, I think we'll be back on by, I plan for us to be back on by 1:45. All right?

And if you are okay with that, I hope you will also be okay with running the trial until 5:00 this afternoon. It may be that you have witness issues, and I understand that isn't going to work because we said we were going to run until 4:30, but I hate to lose that half hour time completely, and I'm prepared to be around until 5:00 if you guys are, but we can talk about that after lunch. But we'll plan to run until 12:15 this afternoon and take our lunch break then.

Okay. You folks have anything for me before we start right into witnesses?

MR. HAUG: No, Your Honor.

THE COURT: No.

MR. HAUG: Other than I'm going to start with some exhibit issues.

THE COURT: Let's take care of that then.

MR. GAERTNER: I just have one issue, Judge, and that is our demonstratives for the next day are due at 6:00 o'clock. And if we run from 4:30 to 5:00, could we have a half hour extension of that so we can get back to the hotel?

THE COURT: I'm sure Mr. Haug will be fine with that. So will I.

MR. GAERTNER: Thanks.

THE COURT: Thank for clarifying that. That's a help, Mr. Gaertner.

MR. HAUG: Good morning, Your Honor. A few things. We have to agreement on a number of exhibits that would be coming in through two depositions that we would otherwise have to play, so because we have agreement, we won't play the depositions. And I'm just going to move those exhibits in, if I may.

THE COURT: You bet.

MR. HAUG: The first is from a deposition of Mr. Roy, and I'll just give the PTX numbers. It's PTX-130, PTX-131, PTX-208, and PTX-235. We offer those four.

THE COURT: Without objection?

MR. GAERTNER: No objection, Your Honor.

THE COURT: Fine. Then admitted without objection.

(Above-referenced exhibits are admitted into evidence.)

MR. HAUG: Thank you, Your Honor. We have a number of exhibits that would be coming through the deposition of Mr. Hothur. H-o-t-h-u-r. Those are PTX-130, PTX-131, PTX-180, PTX-188, PTX-199, and PTX-221.

MR. GAERTNER: I have no objection, Your Honor.

THE COURT: All right. Fine. Thanks. Admitted without objection.

(Above referenced exhibits admitted into evidence.)

MR. HAUG: Thank you. Yesterday, we also reached agreement with respect to admissibility of the ANDA and the NDA to the extent they want to rely on anything in the NDA. And so I would offer now PTX numbers as exhibits from the -- this is all from the ANDA without objection, I believe. And, unfortunately, it is quite a long list. Because the ANDA is not identified as one single exhibit, it's a lot of pieces over the course of time.

THE COURT: All right.

MR. HAUG: So PTX-56 through PTX-92, PTX-93 through PTX-111, PTX-142 to PTX-146, PTX-148, PTX-149 through 151, PTX-153, PTX-155, PTX-156, PTX-158 to PTX-164, PTX-166 to PTX-173, PTX-208 to PTX-212, PTX-217, PTX-282, PTX-287.

THE COURT: Excuse me. Was that 282?

MR. HAUG: 282. Sorry.

THE COURT: Okay.

MR. HAUG: I'm sorry if I'm going too fast.

THE COURT: Okay.

MR. HAUG: PTX-287, PTX-293, PTX-295, PTX-303, PTX-625, PTX-626, PTX-635, PTX-636, PTX-641, PTX-644, PTX-807, PTX-808, PTX-841, PTX-842, and PTX-844. And I'll provide a copy to the Court so that we can double check that.

And the last thing I have, Your Honor, well, I offer all those exhibits.

MR. GAERTNER: No objection, Your Honor.

THE COURT: Thank you. They are admitted.

(Above referenced exhibits admitted into evidence.)

MR. HAUG: Thank you. Last thing, Your Honor, being very mindful of our time constraints for this trial, plaintiffs have decided not to assert any of the secondary factors in this case in anticipation of an obviousness defense here. And so, therefore -- and we have I think reached agreement with defendants on this. There will be no evidence introduced, either fact testimony or expert testimony, with respect to secondary factors, meaning things like commercial success or long-felt need. And so we won't introduce that evidence, and I think the defendants will not need to introduce anything on those issues either.

Is that right?

THE COURT: Well, let me say something on the record here, too.

I think we put the timing of this in consultation with counsel, at least I tried to do that. So I wouldn't want anybody under the impression that you weren't able to put on the case you think you needed to put only, right? So don't -- yeah. For strategic reasons, whatever reasons you have, for choosing to put on or not put on certain evidence, that is up to you. I'm not getting into all of that, but I don't want the timing constraints to become an issue in that regard. Let me just put it that way, right?

MR. HAUG: Thank you, Your Honor. For Shire, no problem. We understand that.

THE COURT: All right. Fine. Thanks.

Mr. Gaertner.

MR. GAERTNER: Oh, understood, Your Honor. Thank you.

Then we will release our experts on commercial success, I take it, Mr. Haug?

MR. HAUG: Yes.

MR. GAERTNER: Thank you, Your Honor.

THE COURT: All right. Good enough.

I think we're ready for witnesses, right?

MR. HAUG: Yes, Your Honor.

THE COURT: Okay. Mr. Lief.

MR. LIEF: We would call our next witness, Dr. Rodolfo Pinal who opines on issues of --

THE COURT: Okay.

MR. ABRAMOWITZ: Your Honor, David Abramowitz.

Before Dr. Pinal gets on the stand, we would like to raise an objection to the demonstratives.

THE COURT: All right. Then, Doctor, why don't you go ahead and have a seat and let me work this out with them.

What did you say your name was again?

MR. ABRAMOWITZ: David Abramowitz for Zydus.

Plaintiffs have proffered Demonstratives 7.7 --

(Court reporter asks counsel to repeat.)

THE COURT: Tell you what. If you are going to make an objection, why don't you come to the lectern. Mr. Lief will cede it to you.

And give me just a moment, Mr. Abramowitz, to get in front of me what it is are objecting to. Okay?

All right. Let's take it from the top.

MR. ABRAMOWITZ: Two nights ago, plaintiffs proposed a series of demonstratives labeled 7.7 to 7.10. They're a series of images that build on each other.

THE COURT: Okay. 7.7?

MR. ABRAMOWITZ: PDX-7.7 to 7.10.

THE COURT: All right. Thank you.

MR. ABRAMOWITZ: And as you'll see, Your Honor, there are images of, it's a DSC tree like the one you saw from Dr. Hanton yesterday that build on each other with a series of color coatings and graphics and dashes and arrows associated with temperatures and different facts.

Do you see that? 7.7 through 7.10. They build on each other.

THE COURT: All right.

MR. ABRAMOWITZ: Sort of like an animation.

THE COURT: So these are the ones that you are talking about?

MR. ABRAMOWITZ: Yes.

THE COURT: Okay.

MR. ABRAMOWITZ: Those are exactly the ones.

This color coding and these dashes and arrows appear to present -- first of all, these graphics and drawings were never presented in Dr. Pinal's expert report and don't appear to be derived from any of the references that he relied on in providing opinions. Instead --

THE COURT: Well, I'm not surprised that the graphics aren't in the expert report. Indeed, I wouldn't have expected that. Demonstratives are not generally in the expert report. They're developed later. But the second point, that's the thing I take it you're really concerned

with.

MR. ABRAMOWITZ: I'm really concerned about the second thing.

THE COURT: Okay. Let's talk about that.

MR. ABRAMOWITZ: And I'm concerned about that because the series of demonstratives appear to be providing a whole new opinion on how to interpret Dr. Henton's DSC that we saw yesterday that is neither in Dr. Pinal's report nor was provided at deposition testimony. Instead, it's sort of a novel interpretation of his DSC. And we're really especially troubled that we were not provided the opportunity in discovery to vet this theory because it provides a level of specificity and detail to his interpretation of Dr. Henton's testing about these are in the report, and not -- as a matter of fact, we specifically examined him, asking for this level of detail and he refused to provide it, and affirmatively testified he could not provide that asserted level of detail.

THE COURT: Well, then what I've really got is the problem with his testimony. I mean, the demonstratives are, I guess, the hook for you to raise that, but your concern is that he shouldn't be able to testify at all about these things. Is that right?

MR. ABRAMOWITZ: Our concern is that these demonstratives lead to that testimony. Last night we

proposed some alterations to the demonstratives that I think would have brought it more in line with the report and the testimony that he offered.

THE COURT: All right.

MR. ABRAMOWITZ: Plaintiffs rejected that and refused to provide any alternatives that would bring it closer to what it is that he has testified about before. So, yes. Our issue is precluding him from offering a brand-new opinion all of a sudden today on interpretation of that DSC.

THE COURT: Right. That's the real issue. You think there's a new opinion in here? Okay. I got you.

Let me hear from Mr. Lief leave in response.

MR. LIEF: Well, certainly, I don't think there's any new opinion in here. Dr. Pinal's opinion, which has been expressed in his report, in his deposition and actually in prior testimony, public testimony in another case, is that there is a dehydration that leads to a melt that leads to a re-crystallization that leads to a further, a further melt.

That opinion, which was a four or five-step opinion, as I understand it --

THE COURT: Well, did he lay those steps out in his report?

MR. LIEF: I think absolutely so. And he talks

about physical rearrangements. He talks about re-crystallizations repeatedly. For instance, in paragraph 39 --

THE COURT: Well, you don't have to start giving me for instances, because I will be hearing from him.

MR. LIEF: All right.

THE COURT: What I expect will happen now is, you know, I'm going to overrule the objection without prejudice. You know, he'll be on the stand. I expect that when you think he's at the point where he's offering testimony that is outside his expert report, Mr. Abramowitz, you'll be on your feet. You can talk to me then.

Mr. Lief, you'd better be ready to show me where it is in the report because if it's not in the report, it's not coming in the record. That's the way it works. Everybody knows it.

MR. LIEF: All right.

THE COURT: Now, that's within the bounds of reason, or I'm not going to say it's not in hoc verba in the report, it's not in here. That isn't the point either. If it's fairly within the ambit of the report, it can come in. If it's not fairly within the ambit of the report, it can't. I expect both sides to be playing by those rules.

Mr. Lief, don't put on something that isn't fairly within the ambit of the report. Mr. Abramowitz,

don't bother objecting if it is fairly within the ambit of the report. Then this will move pretty smoothly.

MR. LIEF: Now --

THE COURT: All right. So -- yes?

MR. LIEF: Thank you.

One specific thing that I think they've objected to in the 7.9 that I think is probably based on their misunderstanding of how we're going to use it, and I can talk to you about that now or we could just go forward.

THE COURT: Let's just get him on the stand. Instead of talking about what he's going to say, let's hear what he says.

MR. LIEF: All right.

THE COURT: This is the advantage of this being a bench trial. In the end, I'm the one that has to make the decision anyway, so we might as well just get it on and talk about it and then argue about what is and isn't fairly in the record. All right.

Let's go ahead and have Dr. Pinal come forward.

... RODOLFO PINAL, having been duly sworn as a witness, was examined and testified as follows ...

THE COURT: Please be seated, Doctor.

THE WITNESS: Thank you, Your Honor.

THE COURT: They have some documents to present to you.

MR. LIEF: If we could approach?

(A binder was handed to the witness.)

THE COURT: I have a copy.

MR. LIEF: Okay.

DIRECT EXAMINATION

BY MR. LIEF:

Q. Good morning, Dr. Pinal.

A. Good morning.

Q. Can we begin? Can you tell us, what is your profession?

A. I am a pharmaceutical scientist and a university professor.

Q. And if we could take a look at PTX-637. Do you recognize this document?

A. Yes. This is my C.V.

Q. All right. And is the information reported in your C.V. accurate and up to date?

A. Yes. As of March 2016, there are some minor updates.

MR. LIEF: We would move PTX-637 into evidence.

MR. ABRAMOWITZ: No objection.

THE COURT: It is admitted without objection.

(PTX-637 was admitted into evidence.)

BY MR. LIEF:

Q. Now, Dr. Pinal, are you currently employed?

A. Yes.

Q. And where are you employed?
A. I am Associate Professor in the Department of Industrial and Physical Pharmacy at Purdue University.
Q. And what do you do in your role as a professor?
A. I conduct research on the physical and chemical characterization of drug products and pharmaceutical materials with a heavy emphasis on physical transformation, such as melting.

I also have taught courses on dosage forms, on solids, pharmaceutical solids and applied thermodynamics.

In addition, I write papers relating to my research on the peer-reviewed literature with a substantial content on phase transformations, such as melting points and associated parameters. And I also serve as reviewer for scientific journals that publish articles in that area of expertise.

Q. And can you briefly describe for us your educational background?
A. Yes. I hold a Bachelor's of Science degree in pharmaceutical chemistry from the National University of Mexico. After that, I obtained a Ph.D. in pharmaceutical sciences with a minor in physical chemistry from the University of Arizona.

Subsequently, I conducted two years of post-doctoral research at the University of Florida.

Q. Beyond the academic world, have you worked in private industry?

A. Yes. I worked for a pharmaceutical company, Hoffman-La Roche, between 1990 and 2003.

Q. And what were your responsibilities at Hoffman-La Roche?

A. I had three jobs while working at the company. The first job was on preformulation, where my responsibilities included the 50 chemical characterizations of new chemical entities. These were newly synthesized compounds that were being evaluated as potential actives for new products.

My second job was in the, in formulation, as a formulation scientist, where my responsibility was in the research and development of dosage forms as well as manufacturing.

My third and most recent job at the company was to -- am I getting some feedback here? Thank you, Your Honor.

My most recent job at the company was a clinical scientist and research leader of the solid state pharmaceutical group. On that responsibility, I had, I had the task of conducting all physical testing and physical characterizations for all active excipients, intermediate blends, and those products, dosage forms that were in the

pre-market, pre-market phase.

As part of the responsibility, I had to determine the melting point of every lot of every active that was either produced or used at the New Jersey facility.

In addition to that, I was responsible for writing the technical content regarding physical characterization and phase transformations that were submitted to the FDA in IND and NDA filings.

And also when the FDA had questions to physical transformations such as melting point, I was responsible for drafting --

THE COURT: Let me interrupt you.

THE WITNESS: Yes, Your Honor?

THE COURT: You said for NDA filings and some other kind of filing.

THE WITNESS: Oh, I'm sorry, Your Honor. Yes. Investigational new drug.

THE COURT: IND.

THE WITNESS: So when the drug is first going to be tested in humans, the submission is an IND.

THE COURT: Okay.

THE WITNESS: And it includes basically the elements of NDA, but in a much smaller scale. And one of the components, the CMC, which is chemistry, manufacturing and control.

THE COURT: All right.

THE WITNESS: Which is the technical part.

THE COURT: Thank you very much.

THE WITNESS: Thank you, Your Honor.

BY MR. LIEF:

Q. All right. And I think you were concluding on what you've done at Hoffman-La Roche.

A. Yes. As I mentioned, when we had questions from the FDA regarding phase transformations, I was responsible for drafting the response.

Q. All right. Have you been accepted as an expert by other federal courts in pharmaceutical science and melting?

A. Yes. In 2013, in the Southern District of Florida, I testified in the case of Shire versus Watson involving the same '720 patent, and as I understand it, the Court accepted my opinion that the magnesium stearate used in Watson's products melted below 90 degrees Centigrade.

Q. All right.

MR. LIEF: We would offer Dr. Pinal as an expert witness in the fields of pharmaceutical science and melting point analysis.

MR. ABRAMOWITZ: No objection, Your Honor.

THE COURT: All right. He's admitted as an expert.

BY MR. LIEF:

Q. Dr. Pinal, what were you asked to do in this case?

A. I was asked to determine whether the melting point of the magnesium stearate and magnesium palmitate in the Zydus ANDA product are lower than 90 degrees Centigrade.

Q. And what have you concluded with respect to those questions?

A. I have concluded that the melting points of both the magnesium stearate and magnesium palmitate of the Zydus ANDA product are lower than 90 degrees Centigrade.

Q. If we could turn to Plaintiffs' Demonstrative Exhibit 7.1, can you tell me what is shown here?

A. This is the Court's claim construction for melting points, and it is -- counsel has advised me that the Court has construed melting points to mean the temperature at which solid and liquid phases of a compound are at equilibrium.

Q. All right. And have you applied this claim construction in coming to your opinions?

A. Yes, I have.

Q. Now, does the Court's claim construction use the exact same words that you had initially proposed for the phrase melting points?

A. No. I had originally proposed the range of temperatures at which a solid begins to liquefy or solid

turns into a liquid. However, the equilibrium temperature is precisely the temperature at which melting can begin to take place. So the two claim constructions are consistent with each other.

The concept of equilibrium gives us the theoretical understanding of what is happening during melting. The claim construction that I proposed was based on the same understanding, but from the point of view of the practical measurement of that temperature.

Q. All right. If you could briefly explain for us the concept of melting.

A. Yes. And I have prepared a demonstrative for that.

Q. And if we could look at PDX-7.2. And can you tell us what this shows?

A. Yes. In this demonstrative on the left-hand side, we have a depiction of a thermometer to indicate the temperature scale, and it has a horizontal bar to mark the temperature where the solid and liquid phases are at equilibrium, to be at a melting temperature. And on the right-hand side we have a representation of crystalline solid material, where the blocks represent organic molecules. A crystal here has two features. One of them is that the molecules are in an orderly arrangement, and, second, that the molecules are locked in position with respect to each other. In other words, they are not free to move due to the

constraints imposed by the molecules surrounding them.

As we increase the temperature, next slide, please, for as long as we are just below the equilibrium temperature, all the molecules would be in the solid phase.

If we further increase the temperature until we obtain precisely that equilibrium temperature, then the thermal energy on the molecules is sufficient, sufficient to allow the molecules to leave the crystal, the crystal phase and go into the liquid, but one special characteristic of the equilibrium condition is that the energy balance is just perfect. In other words, there is no driving force pushing any molecule to stay in one phase or go to the other.

So the molecules are free to choose, so to speak, to be either in the crystal or in the liquid without paying any price, any energy cost. As soon as the temperature surpasses the equilibrium melting temperature, then all the molecules will be in the liquid form.

So if we look at the horizontal bar, whenever the temperature is just below that equilibrium temperature, the sample would be a solid, and if it is just above, it will be a liquid.

So that the melting of crystals can be at higher temperature, but the instant the melting takes place is when we achieve equilibrium. So if we observe melting at a

higher temperature, that is an indication that we have already obtained equilibrium and surpassed it in terms of temperature.

Q. How is melting point determined?

A. In the pharmaceutical field, the most common way for measuring melting point is DSC, differential scanning calorimetry. And what scientists used is, as I mentioned, the equilibrium temperature, the precise temperature at which melting can begin to take place. Scientists use the onset of the melting event of the DSC as a measure, as a measurement of the melting point.

Q. Can a substance have multiple melting points?

A. In general, each solid substance has its own characteristic melting point. However, one common occurrence in pharmaceutical science is that we can take the same sample and subject it to a heating process and observe multiple melting events.

The reason for that is that the same organic molecules can arrange themselves into different solid substances, and each solid substance would have its own characteristic melting point.

So among the different types of solid substances that can be created with organic molecules includes some in which it's not only the organic molecule, but also water molecules are part of the integral structure of the crystal,

and these are called hydrates.

Q. All right. To change to that topic a little bit, can you explain somewhat further what a hydrate is?

A. Yes. And I have prepared a demonstrative to illustrate that point.

Q. If we could look at PDX-7.3. And can you tell us what this shows?

A. Well, here we are using the same representation for the organic molecule, and the circles represent water molecules.

So one important consideration here is that the water present in this solid substance is not water that is simply wetting the crystals, but as we can see, the water molecules are an integral part of the orderly structure.

So what we can see in this case is that both the organic molecules and the water, and the water molecules share the two attributes of the solid crystals. One, that they have an orderly arrangement. And, second, that they are locked in position. So they are immobile with respect to the surrounding molecules.

Q. Can a hydrate crystal, can a hydrate melt?

A. Yes. By heating a crystal, a certain crystal, certain hydrate crystals will melt.

Q. And if we could look at PDX-7.4, is this a demonstrative you prepared?

A. Yes. This would illustrate how a hydrate can melt.

Q. What does it show?

A. Here we have on the left and right-hand sides the same representations as we used in the previous demonstratives.

So as we increase the testimony -- next slide, please -- and for as long as we're again below the equilibrium temperature, the thermal energy is going to bring just vibration into the molecules. That's the way the crystals, they absorb the thermal energy. However, since we are below the equilibrium temperature, the two attributes of the solid crystal remain, and one of them is, again, the molecules' ability to retain their orderly arrangement, and also are immobile in terms of being able to displace themselves with respect to each other.

So, again, if we continue increasing the temperature and we cross the equilibrium temperature, then at that point it forces the thermal energy sufficient to overcome the forces holding the molecule in place and then water can leave, and it breaks the crystalline orderly structure of the organic molecule, giving place to a liquid.

The liquid has two attributes which are in contrast to the solid. One of them is that the molecules are randomly distributed, and the other one is that the molecules have free mobility. They're able to move around

each other, past each other. In other words, they are able to flow.

Q. All right. Now, you mentioned crystals. Can you tell us generally, how are crystals formed?

A. Crystals are formed when randomly, random molecules are able to align themselves with respect to each other to produce an orderly arrangement of the solid crystal. And I have prepared a demonstrative to illustrate that point.

Q. All right. If we could look at PDX-7.5, and can you tell us what this shows?

A. Yes. Here we have on the top and bottom part, we have on the left-hand side the starting crystalline material, and on the right-hand side of both we have the final product after the re-crystallization.

What we have in the middle is up on the top panel, we have the representation of the molecules being in the liquid state, but the liquid is a molten, the molten product is from the crystal on the left.

At the bottom panel in the center we have also the molecules in solution, but the difference, sorry, in liquid state, but the difference in this case is that they are in solution. So the circles in the, in the center pattern at the bottom represent solid molecules which could be water or another solvent.

The similarity between the two panels in the

middle is that the molecules are randomly distributed and, very importantly, they are free to move around each other, so that this allows them to align themselves into an orderly arrangement, giving place to the, to the product, which is the crystal, the crystal on the right-hand side in both cases.

For the bottom example, which is crystallization from solution, we can think of something like honey. You would take a container with honey and leave it on the table for a number of weeks. Eventually, we will see the appearance of sugar crystals. That will be crystallization of sugar from solution.

Q. All right. Again, to change topics a little bit, I would like to discuss magnesium stearate.

If we could turn to PTX-490 as a first --

THE COURT: First a question from me: What is the term "pure crystal" meant to denote?

THE WITNESS: Pure crystal refers in two ways. One of them could be many types of the purity chemically speaking, for example, a high quality crystal, meaning one with no defects. If we have a crystal that is almost perfect, and if I can throw an analogy, it's like we compare a cheap diamond versus an expensive diamond. The difference is that the expensive diamond has fewer imperfections.

So a pure crystal is one that has very few

imperfections, or basically is almost perfect. And for -- by virtue of being almost perfect, what it does is, it squeezes out possible impurities, and it will also result in chemical purity. That is why chemists use crystallization as a means of purification. And what they are trying to achieve is the highest quality, physical quality of the crystal, because the highest physical quality of the crystal will come along with purity.

So, in essence, what chemists do is use crystallization as a purification process, because the molecules, as they arrange themselves, the more perfectly that they can arrange themselves, they are able to squeeze out any molecules which are not like them.

So they go --

THE COURT: The hydrate?

THE WITNESS: The hydrate is part of the structure, so that particular configuration is something that can exist in a pure form, so the organic molecules and water molecules can work in unison, so to speak, to squeeze impurities out. But the highest the physical purity of the chemical crystal would come with the higher chemical purity.

THE COURT: So on the demonstrative where it shows crystal on the left with hydrates included, and crystals on the right called pure crystal and no hydrate,

the difference isn't necessarily that there are no hydrates. It's just a better or purer crystal. Is that what you are saying?

THE WITNESS: Yes. In this context, we talk about pure crystal, we're talking more about the physical quality, the physical perfection of the quality.

THE COURT: All right. Thank you.

THE WITNESS: Thank you, Your Honor.

BY MR. LIEF:

Q. All right. Changing topics a little bit to magnesium stearate in particular, I'd like to turn to PTX-490.

The first question: Can you identify this?

A. Yes. This is the "Handbook of Pharmaceutical Excipients," Second Edition.

Q. All right. And is the "Handbook of Pharmaceutical Excipients" an authoritative reference relied upon by scientists in this field?

A. Yes. It is very widely relied upon by pharmaceutical scientists, including myself.

Q. And if we could take a look at, and turn to page 280, which is also page 490.3. There is Section 4 there.

And can you tell us what it states about magnesium stearate?

A. Well, it says that magnesium stearate consists chiefly of variable proportions of magnesium stearate and

magnesium palmitate.

Q. And if we could turn specifically to the magnesium stearate in Zydus' product. If we could look at PTX-287. And the first question: What is this document?

A. This is the batch manufacturing record for Zydus product, lot EMM196.

Q. All right. And if we could look at page 287.4, what information did you derive from this part of the batch manufacturing record?

A. Well, it identifies magnesium stearate as one of the materials used in this product. It also indicates, identifies Dr. Paul Lohmann as the source of that magnesium stearate, and it also specifies that this material meets the NF, that is national formulary specification, among others.

Q. All right. With that in mind, if we could turn to PTX-644. And do you recognize this document?

A. Yes. This is the certificate of analysis of magnesium stearate supplied by Dr. Paul Lohmann.

Q. Right. And what information do you obtain from this certificate of analysis?

A. Well, if we look at the sixth and seventh lines on the table, it gives the content for stearic acid, and then on the seventh line, stearic and palmitic acid. These are proxies for the content of -- stearic acid is a proxy for

magnesium stearate and palmitic acid is a proxy for magnesium palmitate.

So it indicates that this lost contains 65.5 percent of magnesium stearate and the balance to 98.9 percent, which would be 33.4 percent is magnesium palmitate.

MR. LIEF: All right. To the extent it's not in evidence, we would move PTX-644 into evidence.

MR. ABRAMOWITZ: No objection.

THE COURT: All right. It's admitted.

(PXT-644 Exhibit was admitted into evidence.)

BY MR. LIEF:

Q. Is there any other evidence that shows that the Zydus ANDA product contains both magnesium stearate and magnesium palmitate?

A. Yes. Dr. Hanton testified yesterday. He conducted DCS studies, gas chromatography, mass spectrometry analysis, and this is an analytical technique that separates the chemical and a sample by gas chromatography and identifies them by their specific mass. And the results from Dr. Hanton's analysis are consistent with the results presented here in the certificate of analysis from Dr. Paul Lohmann.

Q. All right. Now, are the magnesium stearate and magnesium palmitate in Zydus's ANDA product in a hydrated form?

A. Yes, they are.
Q. And what do you base that conclusion on?
A. It's based on the results from Dr. Hanton's TGA, that is, thermogravimetric analysis, as well as Zydus's documentation and the literature.
Q. All right. If we could turn to PTX-644 at page .1?
Again, this is a certificate of analysis.
What information does this supply with respect to loss on drying?
A. It gives a value for loss on drying of 3.7 percent. This means that if we were to dry out all the water present in this sample, there will be a reduction in weight of 3.7 percent.
And this result is very consistent with a TGA analysis conducted by Dr. Hanton on this material.
Q. If we could turn back to PTX-490, which is again the Second Edition of the Handbook of Pharmaceutical Excipients. I'd like to look at page 490.4.
And in the left-hand column there under Typical Properties, can you read into the record what is says in the section polymorphism?
A. It indicates that the forms exist as trihydrate and dihydrate, so saying that this magnesium stearate exists in hydrated forms.
Q. Okay. And I would also like to turn you to PTX-497.

And I will ask you as a first matter, do you recognize this document?

A. Yes. This is an article published by Sharpe and other authors titled physical Characterization of the Polymorphic Variations of Magnesium Stearate and Magnesium Palmitate Hydrate Species.

So from the title alone, we can tell both magnesium stearate and magnesium palmitate are known to exist as hydrates.

Q. Is this article from an authoritative journal?

A. Yes, it was published in the journal Structural Chemistry.

Q. Now, Dr. Pinal, was an experiment done to measure the melting point of Zydus's magnesium stearate?

A. Yes.

Q. And what experiment are you referring to?

A. Dr. Hanton, as he testified yesterday, he conducted DSC, differential scanning calorimetry, on the magnesium stearate sample.

Q. And is differential scanning calorimetry a standard they did for determining the melting point of the substance?

A. Yes. As I mentioned earlier, in the pharmaceutical field, DSC is the standard method for determining the melting point of substances.

Q. I'd like to turn you to Plaintiff's Trial

Exhibit 647. As a first question, I'd like to ask you, what is that?

A. This is an excerpt from the USP, United States Pharmacopeia, No. 23, from 1995.

Q. Is USP considered an authoritative reference by people of skill in this area?

A. Yes, it is very widely relied upon source by pharmaceutical scientists.

Q. I'd like you to turn to page 647.5.

We have a section there, (891) thermal analysis. And I'd like to focus you on the left-hand column, second full paragraph, about three lines down, starting with the words "instrumental methods."

Could you read that into the record?

A. Yes. It reads: Instrumental methods have largely supplanted older methods dependent on visual inspection and on measurements under fixed or arbitrary conditions because they are objective, they provide more information, they afford permanent records, and they are generally more sensitive, more precise, and more accurate.

So this supports my previous answer that instrumental methods are the most relied upon ways for determining melting points in the pharmaceutical field.

Q. Just to be clear, is differential scanning calorimetry an instrumental method?

A. Yes, and I did say that for melting point in the pharmaceutical field, it is the premier instrumental method for determining melting points.

Q. Dr. Pinal, have you prepared a demonstrative to help explain Dr. Hanton's DSC results?

A. Yes, I have.

Q. If we could look at PDX-7.6.

What is this?

A. Here, what we see are an exact trace of Dr. Hanton's DSC analysis results. And what we can see, there is two peaks: one starting at about 80 degrees and another one starting at about 125 degrees.

Now, each one of these peaks represents a thermal physical transformation. And the fact that both of the peaks are pointing downward means that they are both in endothermic events, meaning that there was a net gain of energy by the sample on each one of those transformations.

So as we go, looking just from left to right, the beginning, before, we have the starting material which is the Zydus hydrated form of magnesium stearate.

So as it goes through the first transformation, we, and we are located in the middle, so between the two peaks. Once the first transformation is finished, then we have the final product from that transformation which is a different solid substance, made from the same organic

molecules but it is a different solid substance.

So the new solid substance. And as we continue to increase the temperature, it will undergo a transformation of its own.

One of the things to also look in here is that we can see that the first transformation is broad and the second transformation is very sharp and narrow.

Since these are the same molecules present, the analysis of the DSC can tell us what the shape of the second peek tells us what happen. The second sharp peak tells us what happen on the first broad peak.

Q. All right. Just so we understand, the curve that is shown here, where does this come from?

A. This is an exact trace from Dr. Hanton's DSC results and it is indicated on the lower right-hand corner which is PTX-553.

Q. Okay. And can you take us through the various sections of this DSC curve in some greater detail and explain to us what is going on?

A. Yes. So next slide, please.

So what we have at the beginning is the hydrated form of magnesium stearate represented in the bottom using the same representation as in the demonstratives. And before anything happens, all we are doing is just increasing the temperature of that sample.

Then as we approach the transition event -- next slide, please -- we're actually approaching the equilibrium temperature, but the molecules are still locked in position and they are in arrangement. They are vibrating because of the proximity of the equilibrium temperature, but as long as we remain below temperature, the original crystal will remain.

If we further increase the temperature -- next slide -- such that we surpass the equilibrium temperature, and as Dr. Hanton indicated yesterday, he indicated how it is determined from the level of the peak by the DSC instrument, then the water, the water leaves and the dehydration results in the disruption of the orderly structure of the crystal.

So what we have now is that the same organic molecules now are in random, randomly distributed, and also they have free mobility. They are able to move around each other, past each other, and so on. In other words, what we have here is the presence of the magnesium stearate in liquid form.

Now, since the molecules have the ability to move around past each other, they are able to align themselves with each other. And as we continue through the process -- next slide -- they can then align themselves into the new solid substance which is the final product from the

first transformation.

THE COURT: Hold on.

MR. ABRAMOWITZ: I'm going to object at this point, Your Honor. Dr. Pinal has no opinion either in his report and refused to provide an opinion at his deposition that the dehydration, melt, and recrystallization can be separated under the temperature.

MR. LIEF: Just -- and I think this is the point I was going to try to clarify before we began. It is a demonstrative, obviously. There wasn't enough space to the left to put the recrystallization in, too. We are not intending to represent that this recrystallization is occurring at those specific temperatures, so it should not be read that way.

THE COURT: Does that satisfy your concern?

MR. ABRAMOWITZ: If it is on the record, that satisfies my concern.

THE COURT: All right. Fine. Thank you.

You may proceed.

BY MR. LIEF:

Q. Dr. Pinal, if you could continue in your description.

A. Then, when we are in between, on the baseline right in between the two transformations, what we have is the solid form of the final product from the first transformation. And, once again, what we're doing here is increasing its

temperature.

But as we continue to increase the temperature -- next slide, please -- we will obtain the equilibrium melting temperature for the new, for the new product.

The difference that we have between the two solids is that the starting material is the hydrated form, is the form, the hydrated form of magnesium stearate. And the product after the recrystallization is the anhydrous form of magnesium stearate.

Q. Now, Dr. Pinal, why do you conclude that there is a recrystallization occurring?

A. Because the shape of the second peak, this is a very sharp and narrow peak, and that is a characteristic of the melt of a crystal of very high quality, and very pure crystal in the physical sense, in the sense that the molecules are very neatly arranged. And that is the type of crystal that can only be produced when the molecules are freely mobile. They are able to align themselves. It is like making the crystal into one piece as opposed to patching it from different pieces.

So what we can see is a big contrast here is that the second peak is very sharp and narrow, indicating whatever product here was a very high quality crystal and the first peak is actually quite broad.

Q. Now, Dr. Pinal, looking at this, with respect to the first peak, it seems that you are opining that there are several events occurring: dehydration, the melt, and the subsequent recrystallization. Why is there only one peak there?

A. Because what DSC provides is a net balance. And as Dr. Hanton mentioned this yesterday in his testimony, it provides a net balance of energy. And it is a very frequent situation in pharmaceutical systems to have several process taking place very near each other or even overlapping partially or completely.

In these particular case, we have the peak which represents a thermal envelope of the whole transition, so it envelopes all the processes taking place under that envelope.

And in this broad peak, what we have is three processes:

One of them is the dehydration which is endothermic.

Another one is the disruption of the crystalline structure which is basically separating the organic molecules which is also endothermic. And,

We have the crystallization of the anhydrous form which is exothermic.

So we have two contributions that are positive

because they are endothermic and one contribution that is negative because it is exothermic. But the crystallization part is buried under the envelope of the wide first peak.

Q. All right. Is the substance that is melting --

THE COURT: Let me interrupt for a second, Mr. Lief.

MR. LIEF: Yes.

THE COURT: Remind me the technical definition of "endothermic" and "exothermic."

THE WITNESS: Yes, Your Honor. "Endothermic" there, that is one in which from before to after the transition, the sample gained energy.

An "exothermic" event is one in which from before to after the transition, the sample gave up energy.

THE COURT: And the gaining of energy is represented how with respect to temperature?

THE WITNESS: Is by the area of the peak in the direction. So, for example, if we look here at the, on the left-hand side on the baseline where there is the flat baseline, if we had, for this particular type of instrument, an endothermic event in which the sample gains energy, we will see a peak that points downward.

And if we have an exothermic event, we will have a peak that points upward.

So if we have three processes taken together,

what we get here is the algebraic sum of the three peaks. So the three peaks have not resolved.

So we have two negative peaks under this broad peak and one positive peak, but the area of the positive peak is small enough to be basically buried under the larger contributions of the two negative peaks.

THE COURT: All right. Thank you, Dr. Pinal.

THE WITNESS: Thank you, Your Honor.

BY MR. LIEF:

Q. To again focus on the material, the substance that is meting up at 120 or 125 or so, is that the same substance as the magnesium stearate that is in the Zydus product?

A. No. Once we are -- once the first transformation has finished and we are in the baseline between the two peaks, the original substance no longer exists. We have the final product of the first transformation which is a, is the anhydrous form of magnesium stearate, but it is a different substance, a different solid substance, and that is what we see on the melting of the second peak.

Q. All right. Now, beyond the evidence from the DSC, the differential scanning calorimetry, is there any other evidence that supports your opinion that a melt is occurring below 90 degrees C?

A. Yes. The literature of magnesium stearate supports my opinion that there is liquid being formed under the

first, under the first peak. In particular, the fact that dehydration produces the disruption of the three-dimensional crystal structure.

The technical term for this is called the loss of anisotropy.

Q. Just so we have this term, what is anisotropy?

A. Anisotropy is the property of crystals but is not a property of liquids and in the pharmaceutical field is used to determine if a sample is crystalline or not. And I have prepared a demonstrative to help illustrate that point.

Q. Can we take a look at PDX-7.11.

Can you tell us what this shows?

A. This is a depiction how the property of anisotropy is used in the pharmaceutical field to determine if a substance is crystalline or not.

And what we have on the left-hand side, we have the representation of a crystal.

And in the center, in the center panel, we have the representation of a liquid in which we have the molecules in random arrangement.

And on the right-hand side, we have a representation of an amorphous solid in which the molecules are all in a random arrangement.

So the sample is subjected to a filter, which is polarized light. And if the structure of that sample

is orderly, so there is an orderly arrangement of the molecules, the sample will look dark under many angles but at some particular angle, the sample would shine with light, and that is directly the result of the fact that the molecules are in an orderly arrangement.

Conversely, if the molecules are randomly oriented, the samples will appear dark under any angle at which we applied that filtered light, which is polarized light.

Q. And if we could look at PTX-499.

THE COURT: I'm sorry to keep interrupting.

MR. LIEF: That's fine.

THE COURT: If I want to understand this, I have to ask questions.

MR. LIEF: That's fine.

THE COURT: So anisotropy, is that the name that is given to the ordered state or is anisotropy the name given to the testing for it? What does the word itself mean?

THE WITNESS: Your Honor, anisotropy means in a solid material, the properties are not the same in the vertical direction or horizontal direction or back and forth direction. So it doesn't have the same properties. So, for example, it may be easier to compress in one direction than another, or the light would go faster in one direction than

the other.

So that is what anisotropy means. That on a solid material, the properties are not -- if you measure a property, such as speed of sound, speed of light, mechanical resistance -- it will not be the same if you do it either horizontally or vertically.

If the molecules are randomly distributed like in a liquid, the properties will be the same regardless of which angle you are testing them.

THE COURT: So if you say, oh, this thing is anisotropic --

THE WITNESS: Anisotropic, correct, Your Honor.

THE COURT: -- that would mean there's some orderly arrangement to it?

THE WITNESS: Exactly.

THE COURT: It's a way to determine if something is a crystal?

THE WITNESS: Exactly. It is used very frequently to do that. If a material exhibits anisotropy, it is the result of molecules having an orderly arrangement.

THE COURT: All right. Thank you. I appreciate that.

THE WITNESS: Thank you, Your Honor.

BY MR. LIEF:

Q. If we could turn to PTX-499.

And as a first matter, I'll ask you what is this article?

A. This is an article published by Ertel and Carstensen, entitled An Examination of the Physical Properties of Pure Magnesium Stearate.

Q. And in what journal is this published?

A. In the International Journal of Pharmaceutics.

Q. Is that an authoritative journal people of skill in this area turn to?

A. Yes, it is one of the most highly reputable journals in the pharmaceutical field.

Q. If we could turn to internal page 171, which I think we have, otherwise numbered as 499.2.

In the summary of the article, what is stated about four lines down?

A. It indicates that the loss of water hydration resulted in the disruption of the crystal 3-dimensional lattice structure.

And this is an important statement on two accounts. One of them was that it made it to the summary section or abstract, as we call it in the U.S., because as we can see, this is a very short paragraph where the authors capture what they consider to be their most significant findings or observations from their study.

Second, it provides substantive evidence that

the dehydration of magnesium stearate is a violent event that disrupts the crystal structure of magnesium stearate.

Q. All right. And if we could turn to page 499.5 in the Ertel and Carstensen article, which is internal page 174.

And, again, look at the left-hand column. I think it is about eight lines down.

Can you tell us what it says there?

A. It says that the loss of moisture was accompanied by a darkening of the crystals' appearance when viewed under cross-polars, indicating a loss of their anisotropic property, which had also been reported by Miller, among other authors.

Q. Again, what is the significance of loss of anisotropy during the dehydration process?

A. It signifies the formation of the liquid. Because crystals have anisotropy, liquids do not.

Q. Just as a check on that, in your demonstrative on anisotropy, on the right-hand side, there was an example of a solid, an amorphous solid that also didn't have anisotropy. Why would you conclude it is a liquid and not a crystal?

A. That is true. But the difference between amorphous solids and liquids is that in amorphous solids, the molecules are locked in place so they share the inability, the inability to move each other and align themselves with

a crystal. So it is, the liquid is where the mobility exists.

Q. Now, we look at Ertel and Carstensen and we looked at the Sharpe paper briefly. Did those papers conclude that the first peak represents a melt?

A. No, they limit their discussion to the dehydration process taking place, which indeed is taking place.

Q. So do you disagree with those papers?

A. No, I agree as far as they go. In fact, their analysis is part of my opinion, but it is only part of my opinion because it is not it a complete analysis. They didn't explore, for example, what is the relationship between the first and second endotherms, which are basically the same sample and the same molecules.

Q. Is the melting point of pure magnesium stearate below 90 degrees C?

A. Yes, it is.

Q. I'd like to turn back to Sharpe, which is PTX-497. And if we could look at page 76, which is also 497.4.

There is a Figure 2 there. And can you tell us what this shows?

THE COURT: I'm sorry to interrupt but the use of the word "pure" there has got me thrown a little bit.

When you say the pure magnesium stearate melting point is below 90, are you referring to what on the

demonstrative was labeled as the hydrated or Zydus product magnesium stearate or what are you referring to?

THE WITNESS: Your Honor, the Zydus magnesium stearate is a mixture of different chemicals. The main components, one of them is magnesium stearate. The other one is magnesium palmitate. So they both exist in the Zydus, on the Zydus product.

Now, when we talk about pure magnesium stearate in this, in this question, it refers to the magnesium stearate that is free from magnesium palmitate.

THE COURT: All right. And so my question is -- I ask a lot of questions. I'm taking your time on your clock. Sorry about that. You showed a demonstrative in which you showed an arrangement of blocks to represent the molecule, and you said, and you called it, in a certain frame anyway, you called it a pure crystal. That is also represented on the demonstratives as the form, representing the form of the magnesium stearate after it passes the first peak. Right?

THE WITNESS: (Nodding yes.)

THE COURT: Okay. So when you say the pure magnesium stearate, you are not -- are you trying to say the magnesium stearate after it goes through the first transition or do you mean the magnesium stearate before?

THE WITNESS: Your Honor, thank you. And I

apologize for the lack of clarity, but hopefully I will be able to clarify it now.

What happened is that the label of the material that Zydus uses is magnesium stearate, which is in fact a mixture of chiefly two substances. So in the demonstrative, when I referred to the pure crystal, maybe in the context is more like a more perfect crystal.

THE COURT: Right.

THE WITNESS: A physically pure, physically perfect crystal.

THE COURT: Sure. So I'm just clarifying. Your use of the word "pure" is equivocal here. In one instance, you are talking about a pure crystal, in the other you are talking about magnesium stearate without magnesium palmitate. Have I got you right?

THE WITNESS: Yes, Your Honor.

THE COURT: Okay. Fine. Thanks. Go ahead.

BY MR. LIEF:

Q. And again, in Sharpe, we're looking at Figure 2. I guess in light of those questions, as a first question, are the DSC and TGA traces here of a sample that is magnesium stearate alone?

A. Yes. This is magnesium stearate alone, free from any magnesium palmitate.

Q. All right.

A. And what we see is the overlay of the TGA on top and DSC traces on the bottom. And one of the things that -- and this is for the hydrated form of magnesium stearate, hydrated form alone. And what we can notice is two things:

One of them is that these results are both TGA and DSC analysis are very similar to the results obtained by Dr. Hanton in his analysis.

And, in addition, if we look on the bottom trace, at the onset of the first peak, we can see that the onset of that first peak is below 90 degrees centigrade, and this is for magnesium stearate alone.

Q. All right. Now, the same question with respect to magnesium palmitate alone. Does it melt below 90 degrees C?

A. Yes, it does.

Q. If we could turn in the Sharpe paper to internal page 78, which is 497.6.

And if we could look at Figure 5.

Can you tell us, first, are the traces that are in Figure 5 here for magnesium palmitate alone or something else?

A. No, these are traces similar to the previous example of the TGA and DSC for magnesium palmitate alone, meaning free from any magnesium stearate. And,

Once again, what we can see from this sample is that the TGA results are very similar to those obtained by

Dr. Hanton in his analysis.

In addition, we can also see that the onset of the first peak on the DSC, which is on the bottom trace, is lower than 90 degrees centigrade.

So from these two figures, we can see that the melting point of magnesium stearate alone is below 90 degrees centigrade and the melting point of magnesium palmitate alone is below 90 degrees centigrade.

Q. What about the sample with the mixture from Zydus?

A. From the DSC from Dr. Hanton's analysis, we can see when they are combined, the peak also has a melting point below 90 degrees, which was about 82 degrees, the onset temperature.

Q. Is there any other evidence that supports your opinion that magnesium stearate melts below 90 degrees?

A. Yes, there are numerous sources in the literature that indicate that the melting point of magnesium stearate is lower than 90 degrees centigrade.

Q. All right. If we look at PTX-491, the first question. What is this?

A. This is the Handbook of Pharmaceutical Excipients. This is the -- let me see -- the first edition.

Q. All right. And if we look at PTX-491.4, I'd like you to look at the left-hand column under typical properties.

What does it report for the melting point of

magnesium stearate?

A. 88.5 degrees centigrade.

Q. And what year was this published?

A. 1986.

Q. I'd now like to go to the book we already looked at, the second edition of the handbook, PTX-490, and focus you on page 490.4.

Again, left-hand column, typical properties. What is the melting point reported?

A. 88.5 degrees centigrade.

Q. And what year was that published?

A. In 1994.

Q. All right. Now, did the subsequent editions of the Handbook of Pharmaceutical Excipients report that same melting point for magnesium stearate?

A. No, they report higher temperatures, about 120 degrees or higher.

Q. And what do you believe they're reporting there?

A. Well, as we can see from the Dr. Hanton's results, that higher melting temperature corresponds to the anhydrous form of magnesium stearate.

Q. All right. If we could look at PTX-506.

Can you tell me what this document is?

A. This is the McGraw-Hill Dictionary of Scientific and Technical Terms, the Fifth Edition.

Q. Now, is that an authoritative text that is looked to by people of ordinary skill in this art?

A. Yes, it is. And I have used it in the past.

Q. Now, if we turn to page 506.3. And I would direct you to the right-hand column, there is an entry for magnesium stearate.

And what does it report for the melting point of magnesium stearate?

A. 89 degrees centigrade.

Q. All right. And what year was this published?

A. Bear with me.

1994.

Q. Again, looking at PTX-657, can you tell us what this is?

A. This is Hawley's Condensed Chemical Dictionary, 13th Edition.

Q. Is that an authoritative text that is looked to by people of skill in the art?

A. Yes, it is.

Q. If you look at page 657.4, this is, in the left-hand column, it is the bottom entry on the bottom line. What melting point is reported for magnesium stearate there?

A. 88.5 degrees centigrade.

Q. And what year was this published?

A. 1997.

Q. And I'd now like to look at PTX-656.

What is this book?

A. This is Ash's Handbook of Pharmaceutical Additives, Second Edition.

Q. And is this an authoritative textbook looked to by ordinary people of skill in the art?

A. Yes, it is.

Q. If we turn to PTX-656.3. Left-hand column is an entry is a magnesium stearate.

In the section for properties, what is reported for the melting point?

A. 88.5 degrees centigrade.

Q. What year was this published?

A. 2002.

Q. I'd like to turn you to PTX-507.

What is this?

A. This is the McGraw-Hill Dictionary of Scientific and Technical Terms, Sixth Edition.

Q. And if we look at page 507.3. In the left-hand column, the entry for magnesium stearate, what is reported as the melting point?

A. 89 degrees centigrade.

Q. And what year was this published?

A. 2003.

MR. LIEF: Thank you. No further questions.

THE COURT: Mr. Abramowitz, your cross-examination, please.

MR. ABRAMOWITZ: Your Honor, may I approach?

THE COURT: You may. Actually, give me just a just a moment.

The Court Reporter: I'm fine. Thank you.

THE COURT: Please.

(Binders passed forward.)

MR. LIEF: Your Honor, a housekeeping matter. I apologize. In PTX-497, we referred to Figure 2 and Figure 5, and we had an agreement with the other side that under Rule 803, I think it is .18, that we will agree that figures from learned treatises and learned articles can be admitted themselves. So we would move that PTX-497, Figure 2 and Figure 5 will be admitted.

MR. ABRAMOWITZ: No objection to the figures.

THE COURT: All right. They're admitted without objection.

(PTX-497, Figures 2 and Figure 5 are admitted into evidence.)

CROSS-EXAMINATION

BY MR. ABRAMOWITZ:

Q. Now, Dr. Pinal, earlier you testified that your construction of the term "melting point," which is the beginning of when a solid turns into a liquid is consistent

with the equilibrium of a temperature of a solid to a liquid; is that correct?

A. That's correct.

Q. Now, am I correct that melting is a phenomenon at least at the point where the free energy of the particles in the liquid state, so the energy of the particles of the liquid state is equivalent to the particles in the solid state?

A. Could you -- you used the term "particles." Can you clarify?

Q. In the equilibrium state, melting point state, the free energy of the liquid molecules is equivalent to the free energy of the solid molecules; is that correct?

A. Yes.

Q. And am I correct that at the beginning of when a substance begins to liquify, there is not an equivalent number of liquid and solid molecules present?

A. When the equilibrium temperature is obtained, the molecules have the same, the solid or liquid molecules have the same free energy. Means that they have no driving force to go in either direction. So there would be no energy cost on doing that. So they would be free to go and, at that point, both phases, solid and liquid coexist, and they coexist in equilibrium, so you would have them both.

So the first appearance of the liquid is precisely when the equilibrium temperature is obtained, not before.

Q. So the first appearance for the liquid, when there is a small amount of liquid, is when the free energy between the solid and liquid is equal in your opinion; is that correct?

A. That is when it first appears. And since the molecules are free to choose, it can be a small amount, it can be a large amount. There is no determining the proportion because there is no tax, energy, so to speak, when they do that. So there is no constraint to whether there is many or few.

Once they are in equilibrium, the molecules are blind, so to speak, to whether they're in the solid or they're in the liquid.

Q. Now, you are relying on the DSC Dr. Hanton performed; is that correct?

A. That is correct.

Q. Am I correct DSC is not a visual test?

A. No, it is not a visual test. It is an instrumental test. And as we saw from the USP, they are preferred over visual tests.

Q. Why don't we turn to the USP exhibit that you rely on, PTX-647.

A. Oh. Mine?
Q. In your opening binder.
A. (Witness complies.)
Q. And am I correct that on page PTX-647.3, internal page 1805 of the USP, it specifies a test for melting range or temperature?
A. Correct.
Q. And am I correct that this test is a visual test, a capillary melting point test; is that correct?
A. It is a visual test, yes.
Q. So regardless of the fact that the instrumental method section you talked about earlier in your testimony exists in the USP, the official USP official test for range of temperature remains a capillary visual test; is that correct?
A. In the USP, yes. However, when we talk about a melting range, we are talking about a multiplicity of temperatures, aside from the claim construction for melting point is a specific temperature.

So if we start talking about ranges of temperatures, it could be an infinite number of different temperatures in a range, the question is how can we basically apply the claim construction of this case when we talk about one temperature.

So the way I see it, when we talk about ranges

of temperatures, in a way that contravenes the claim construction.

Q. Now, in coming to your opinions regarding Dr. Hanton's test, you are relying solely on the DSC; is that correct?

A. Yes. As I stated before, DSC is the most widely used method in the pharmaceutical field. And as per the USP, it's an instrumental method that the USP indicates that instrumental methods have supplanted visual methods precisely because of the subjectivity of the visual methods.

Q. And am I correct that the endotherms that display on Dr. Hanton's DSC are -- well, strike that.

Why don't we start with, are endothermic processes in a DSC, are there ones other than melting?

A. Yes. Actually, as we mentioned in Dr. Hanton's, the demonstratives from Dr. Hanton's results, there, we have two. One of them is dehydration, which is endothermic. The other one is melting, which is also endothermic.

Q. So am I correct that dehydration without melting is also endothermic?

A. Dehydration without melting is also endothermic.

Q. Am I correct what we call solid transitions, transition from one solid state to another solid state, are endothermic?

A. It depends which one is the stable form. When you

have solid-solid transitions, there are -- and I don't want to get too technical, but depending if it is happening, you have a method. The method stable phase is the stable one if you are over or below a transition temperature. And we are getting a little bit sort of out there. There is no problem. I can continue.

So the solid-solid transitions can be either endothermic or exothermic, depending on the type of system you have.

Q. And am I correct that the simple presence of a DSC on a endotherm doesn't mean a melting curve?

A. Say that again.

Q. Am I correct the simple presence of a DSC on an endotherm on the trace does not mean a melting curve?

A. No, an endotherm means a net gain of energy by the sample, and all melts would have that.

Q. So you have to interpret the DSC to determine if there is a melt; is that correct?

A. That is correct.

Q. And that interpretation often requires the use of other methods such as TGA and hot stage microscopy; am I correct?

A. The TGA is used to follow the evolution of volatile materials such as water when they are hydrated. And the hot stage microscopy is a visual method, you know, sometimes is

used to look at the sample how it melts. But in terms of the sensitivity, there is no comparison in between any visual method and an instrumental method.

Q. Dr. Pinal, can I take you to DTX-2005 in your binder?

A. (Witness complies.)

Q. DTX-2005 is the Handbook of Pharmaceutical Analysis. Do you see that?

A. Yes, I do.

Q. Is that an authoritative text in the industry?

A. Yes.

Q. And if we turn to the first page on the interior of the Handbook of Pharmaceutical Analysis, you will see this version was published in 2002. Is that correct?

A. Yes. I see it.

Q. And so this version was published after the USP that you talked about; is that correct?

A. Correct.

Q. Turning to article 1, you will see an article on the next page entitled Form Selection of a Pharmaceutical Compound, by two authors, Ann Newman and G Stahly. Do you see that?

A. I see that.

Q. Are you familiar with Dr. Newman?

A. I know the book.

Q. And Dr. Newman is one of the authors of the Sharpe

papers you talked about earlier; is that correct?

A. Yes.

Q. And Dr. Stahly is a well known expert in the field of solid state chemistry; is that correct?

A. Yes.

Q. If we turn to the fifth page in section B on Thermal Methods.

A. Sorry. Section B?

Q. Section B.

A. Oh, yes.

Q. Do you see where Drs. Newman and Stahly stated the thermal method of analysis discussed in this section are differential scanning calorimetry (DSC), thermogravimetric analysis (TG), and hot stage microscopy. All three methods provide information upon heating the sample. Heating can be static or dynamic in nature, depending on the information required.

Did I read that correctly?

A. Yes.

Q. If you go three more paragraphs down, do you see where Dr. Stahly and Dr. Newman state: The observance of thermal transitions by DSC is insufficient to fully characterize the behavior of a substance on heating. It is not known if an endothermic transition observed in the DSC is a volatilization or a melt without corroborating

information, such as TG or HSM data. It is important to understand the origin of the DSC transitions to fully characterize the system and understand the relationship between various solid forms.

Did I read that correctly?

A. Yes. And let me tell you a little bit about the context of this.

This is, in the pharmaceutical industry, there is thousands of compounds that are newly generated every year and they have to be subjected to thermal analysis when they have never been seen by any laboratory. So this statement is general for how it is done in the pharmaceutical industry. And when you have a material that you have never seen, you cannot go and assert that just because you see an endotherm you have a melt.

Actually, people who are not experienced made that mistake quite often.

So this statement is right on the money in the sense that when you have no prior information about the compound, you cannot assign endotherm or exotherms just arbitrarily.

In the case of magnesium stearate, we have decades of literature. We have analysis and published information that tells us what is happening. And one of the points that there is no disagreement in this case

between both sides is that once we are at 125 point, there is a melt. So in that sense we have an agreement.

And the reason for that is that there is already information in the literature, and information collected in the laboratories tells us that.

So what we can tell in this sample, that that second endotherm is a melting. So now the first endotherm is in dispute, but we agreed on the second one.

Q. Why don't we turn to PTX-499, the Ertel and Carstensen article you relied on. It's in your cross binder as well. It's in both.

A. Oh. So what number would it be?

Q. PTX-499.

A. Okay.

Q. If we go to internal page PTX-499.3, which is reference page 172, in the bottom right-hand corner, do you see the reference to thermal properties?

A. Yes, I see that.

Q. And below thermal properties, it stretches on to the next page, 1723, 499.4.

A. Okay.

Q. Am I correct that Ertel and Carstensen sets forth the thermal test that they use on the magnesium stearate and magnesium palmitate samples?

A. Could you repeat your question, please?

Q. Am I correct here in the thermal properties section, Ertel and Carstensen set forth the thermal test they used on magnesium stearate?

A. Yes.

Q. And am I correct that they ran not only a DSC but also a TGA and a hot stage microscopy experiment on their sample of magnesium stearate?

A. Correct.

Q. Now, earlier, if we look at page 174 of that article, you testified concerning the loss of anisotropy. Am I correct?

A. Correct.

Q. And in that section on page 174, in the first paragraph on the left, the sentence referenced by you in your opening testimony references an article by Miller from 1985. Is that correct?

A. Correct.

Q. And am I correct that you relied on this Miller article also known as Miller and York in forming your opinion?

A. Yes, I did.

Q. But you didn't present that article in your opening testimony, is that correct?

A. No.

Q. If we go to PTX-504.

Do you see the Miller and York article?

A. Yes.

Q. And this is from the International Journal of Pharmaceutics. Is that an authoritative journal in the industry?

A. Yes, as I stated earlier today.

Q. And if we go to page 58, PTX-504.4, there is a section on thermal analysis; correct?

A. Correct.

Q. And in this thermal analysis section, Miller and York represent that they conducted both DSC and TGA; is that correct?

A. Correct.

Q. And then there is a section below the thermal analysis section called thermal microscopy. Do you see that?

A. Yes, I see it.

Q. Am I correct that in this thermal microscopy section, Miller/York report that they also conducted a hot stage experiment? Is that correct?

A. Correct. And if we look at this paper, also the previous one by Ertel and Carstensen, we see a common theme in the use of hot stage microscopy.

Both of them use hot stage microscopy to assess the initial anisotropic properties of the material because

that provides information of what is happening at the molecular level and they use DSC as the instrumental method for determining temperatures.

Q. First I want to point you to Figure 2 of Miller and York on page 61. Am I correct that Figure 2 presents DSC or differential scanning calorimetry for magnesium stearate and magnesium palmitate samples?

A. Yes.

Q. And powders A and B are the magnesium stearate; am I correct?

A. Correct.

Q. And powders C and D are the magnesium palmitate; am I correct?

A. Correct.

Q. Am I correct that Miller and York assigned in the top left, powder A thermogram, the first two endotherms only to dehydration?

A. Yes, and the same as Ertel and Carstensen. As I mentioned, they limited this code of this discussion to the dehydration taking place under that endotherm which indeed is taking place.

Q. And like you did, they assigned the final endotherm to the melting of the anhydrous form; am I correct?

A. Correct.

Q. If we look at Figure 3, this presents differential

thermograms of magnesium stearate and magnesium palmitate that were dried at 90 degrees C; am I correct?

A. Yes.

Q. And Miller and York assigned these endotherms to melting events; is that correct?

A. Correct.

Q. However, the dried magnesium stearate do not show any endotherms below 90 degrees C; is that correct?

A. We need to clarify this because otherwise we're going to rely on something that is wrong.

These samples, they were dried at 90 degrees. That means they were placed in an oven, in a heating place to heat it which is above the melting temperature of the hydrated form of magnesium stearate.

So what happen is that the same process, as we saw from Dr. Hanton, DSC took place without any instrument monitoring the evolution of heat.

So if you looked over some period of time, what these represent is if we go back to the demonstrative or the data from Dr. Hanton, we're right in the middle in between the two endotherms.

When we have the final product of dehydration which took place by the melting of magnesium stearate, the disruption of the crystalline structure, and the recrystallization, then once that sample is taken out of

the oven at 90 degrees and it is placed under DSC, of course, it has to show a melting point of 120 degrees or so. Because it is the anhydrous form, which is exactly what we have seen from Dr. Hanton's analysis and other literature.

So it doesn't show it below that is because it was exposed at 90 degrees in a chamber. That is how it is done.

Q. Dr. Pinal, am I correct that Miller and York do not report seeing melting during the process of drying the magnesium stearate samples?

A. During the?

Q. Process of drying of magnesium stearate at 90 degrees C?

A. The process of drying is not for determining a melting point, is not even a visual method for melting point. You take a tray of material and put it in an oven and close the door. It is not designed for that. So they could not possibly claim that they saw it. They didn't see a melting because it was -- you know, that's how the instrument look. Is not designed for that.

Q. Well, am I correct that the Miller and York did produce one experiment that looked at the crystals during the thermal transitions?

A. Yes, they did.

Q. Okay. And can we look at Figure 5, which is the thermal microscopy experiments in Miller and York?

A. Um-hmm.

Q. And am I correct that the crystal Miller and York are looking at is what we call rhombohedral plate?

A. Correct.

Q. And am I correct that through a temperature of approximately 121 degrees C, that rhombohedral plate maintains its shape?

A. Yes. That part of the sample remains, maintains its shape.

Q. And am I correct that Miller and York do not report visually seeing any liquid between 88 degrees and 121 degrees C?

A. No, but they provide information that indicates that there was a liquid form. They do report the loss of anisotropy under those conditions. That actually is more telling than looking at by eye.

But even then, for example, if you look at this -- and this is one that shows why visual methods are so subjective.

If we look on the panel at 88 degrees, you know, we look at this, this is like a little cross, like a diamond with a cross.

Once we go to 96, they are fused.

So that means there were changes. But this is where it is so small scale where there was liquid, there was fusion between the two. This is what we can tell. This is what by looking by eyes, by eye indicate. Right?

And, of course, it doesn't change the test because the liquid is viscous enough. And we can program because we need to go to very high temperature in order to make it a running liquid. A liquid, not every liquid is a very running liquid like alcohol, for example. There are some very thick liquids and organic melts are good example of highly viscous liquids.

Q. Can we turn to Page 64.

A. Sorry. Which?

Q. Page 64, 504.10.

A. Okay.

Q. In the first full sentence, am I correct that Miller and York refer to Figure 5 and state the loss of moisture in these cases was accompanied by the appearance of diagonal striations on the particles, shown occurring for magnesium stearate B at 96 degrees C?

A. Yes, and that is where they actually took that picture. And that is again when you have differential scanning calorimetry, which is an instrumental method, you are scanning the temperature.

So these, they didn't know in advance what they

were going to obtain, so they decided to take a picture of 96 degrees. So the fact that they took the picture of 96 degrees. It doesn't mean it didn't happen until 96. They capture how it was at that temperature, but it doesn't mean that that is when it began or that nothing happened before that.

And, once again, this, you know, visual methods are helpful, but they're only helpful, and that is why they have been supplanted by instrumental methods.

What we want to see is what happened at 96, 94, 93. We need an instrumental method like DSC because that provides that type of information.

Q. But am I correct Miller and York had the benefit of this hot stage microscopy showing loss of anisotropy and still do not report the first endotherm in their DSC as a melt?

A. No. And as I said before, authors like Miller and York as well as Ertel and Carstensen, they limited the scope of the discussion to the dehydration component of that first endotherm. And that is a part of my opinion.

MR. ABRAMOWITZ: Your Honor, at this time we'd like to move in Figures 2, 3, and 5 of PTX-504.

MR. LIEF: No objection to that.

THE COURT: All right. They are admitted without objection.

(Figures 2, 3, and 5 of PTX-504 are admitted into evidence.)

THE COURT: I'm going to ask counsel, since, well, you will help us keep track. You have marked the entire document with an exhibit number, and you are actually admitting only a part of the document.

So you will probably make the record a little bit clearer somehow if you excerpt what is actually in the record. Are you getting at what I'm getting at?

MR. ABRAMOWITZ: I think I understand, yes.

THE COURT: Give it its own number. I'm taking it that this PTX-504 is not going in in its entirety. You are using that as a mark for identification, but you have got now excerpted certain figures that you want in, so I'm just asking the parties to help keep the record clean by creating the exhibits which are the ones to be admitted in their entirety.

MR. ABRAMOWITZ: I think we can provide sub-numbers associated with that that we can do.

THE COURT: Whatever you want to do, just so our record is clean.

MR. LIEF: That's fine.

THE COURT: Thanks.

BY MR. ABRAMOWITZ:

Q. Now changing direction a little bit. Earlier today,

you described the phenomenon that happens under the first endotherm in Dr. Hanton's test as first a dehydration and then a melt; is that correct?

A. Yes. The dehydration occurs and then we have the crystalline structure which is the melt, yes.

Q. Am I correct, it is your opinion that after the melt occurs, there is magnesium stearate present in a liquid state?

A. Correct.

Q. And that magnesium stearate present in the liquid state only has magnesium stearate. The water has left the system; is that correct?

A. Yes, the water has left the system. It has the ability to. It is a volatile material, yes.

Q. So the melt itself is not a hydrate, it's just the molecule magnesium stearate in another form; correct?

A. After at a higher temperature, because, remember, the equilibrium temperature is when the molecules have no driving force to stay in one phase or go to the other, either way.

So when the molecules are precise equilibrium temperature, all the molecules are present. The instant that we exceed that equilibrium temperature, then we are already surpassing the equilibrium value, and then the molecules would be as a melt. So the melt, when it first

appears in equilibrium is the melt of the hydrate. And then when water leaves, it's the melt of the magnesium stearate.

Q. Now, I want to make sure I got this straight because you referred to the melt and the liquid. Am I correct that your opinion is that during the first endotherm in Dr. Hanton's DSC, Zydus's magnesium stearate forms a mesophase or liquid crystal at temperatures below 90 degrees C?

A. Can you repeat the question, please?

Q. Am I correct that it is your opinion that during the first endotherm in Dr. Hanton's DSC, Zydus's magnesium stearate forms what is called a mesophase or a liquid crystal below 90 degrees C?

A. No, and let me tell you why. Mesophases are liquid crystals, have order. The molecules are orderly arranged. And if they, if it was a mesophase or a liquid crystal, with the sample would exhibit anisotropy. Anisotropy is an indication of whether or not those molecules have some order or not. And the reports indicate that they do not.

So it is not a mesophase or a liquid crystal, it is a liquid. Because liquids do not have anisotropy, crystals have anisotropy. Liquid crystals have anisotropy. Mesophases have anisotropy.

The only phase that does not exhibit anisotropy is the liquid when they are truly randomly arranged.

Q. Dr. Pinal, do you recall being deposed in this case?
A. Yes.
Q. And were you under oath at that deposition?
A. Yes, I was.
Q. Was I present at the deposition?
A. Yes, you were.
Q. Could you turn in your binder to page 104 of your deposition.
A. Um-hmm. Was what number is it?
Q. It is in your binder. The deposition is referred to as 8.1.
A. Okay.
Q. Looking -- tell me, are you at 104?
A. I'm here. Yes.
Q. Looking at your testimony from lines 10 to 17, it states:

"Question:

A. And which page?
Q. Page 104.
A. Okay.
Q. "Question: Is it not your opinion that at temperature below 90 degrees C, Zydus's magnesium stearate forms a mesophase; correct?

"Answer: The liquid produced upon melting below 90 degrees could be referred to by some people as a liquid

crystal or sometimes called also mesophase."

Did I read that correctly?

A. Yes, because in the literature they do that quite often. If you go to the literature, many people call that a mesophase, so people do refer to that as a mesophase.

That doesn't mean it is my opinion that it is a mesophase, but if you will find it. You will find people claiming that it is a mesophase.

Q. Am I correct that a mesophase is a solid?

A. A mesophase is, well, some people consider a mesophase a solid and some people call it liquid crystals, so it depends on that.

The common thing that they have is that they have orderly structure. They have order in the molecules.

And going back to your question, yes, some people, you go through it, you will find people who call, basically claim that there is a mesophase in there, but mesophases will exhibit anisotropy.

Q. Does a mesophase only exhibit anisotropy in one or two directions as opposed to three?

A. Anisotropy is not like that. Anisotropy is not in different directions. The properties are different in different directions, but the anisotropy is only one secondary, one extra I beam.

And I'm getting a little bit technical here, but

it is not that you get one for every direction. When you have properties that are different in every direction and you apply the filter light, the polarized light, if the system is isotropic, the light just go straight and nothing will happen. It will only be slowed down by the sound.

If the molecules have any order in them, you would get a second that would be twisted, it will be sort of like rotated, and that is why it would show on the cross curve polars. So it is not the anisotropy you would get one for every. So you get a primary, you get what they call the ordinary rate and the extraordinary rate, but that is a result of order, it is not of the directions.

Q. Am I correct there are crystals known as uniaxial crystals which under cross polars do not show -- which show anisotropy in one direction?

A. Yes, but that would be a single crystal. And we have to differentiate between the single crystal and a single particle because the difference is very, very big. A single crystal is one single particle in which all the molecules are part of the same grain. Basically, every single molecule. If you have a crystal like that and you happen to align it, you know, to the light, you could see that.

But the crystals would grow in nature and even other forms, they don't grow like that. They are polycrystalline. They are multiple crystals that collide

with each other in every single direction.

So in order for the alignment that the instrument could take place with mesophase, which is a natural product, would be the vegetable or the plant was able to produce like every single molecule in the same direction so that all the crystals happen to be of the same grain. And that is just impossible. That doesn't happen in nature because it is extremely difficult to do in the laboratory.

As a matter of fact, right, it is well known that nobody so far has been able to produce a single crystal magnesium stearate. A single crystal is a requirement for determining basically without any doubt what is the crystalline structure; and the reason there is so much question about it, nobody has been able to produce precisely what you indicate that could happen.

Q. Can you turn in your binder to PTX-498, the Rajala and Laine article?

A. (Witness complies.)

Q. Dr. Pinal, this article appears in Thermochimica Acta. Is that a well known and respected journal in your field?

A. Yes, it is.

Q. And it is an authoritative journal on physics; is that correct?

A. On basically thermal analysis more than physics.
Q. And am I correct you relied on the Rajala and Laine article in forming your opinion?
A. Correct.
Q. Am I correct that Rajala and Laine studied two commercial batches of the magnesium stearate where the magnesium stearate and magnesium palmitate were mixed?
A. Correct.
Q. And those are batches A and B; is that correct?
A. Correct.
Q. Now, am I correct that Rajala and Laine conducted hot stage microscopy?
A. Yes. And by the way, they also report the loss of anisotropy.
Q. I'm getting right to that. Can we turn to PTX-498.7, which is internal page 183.

Looking at the sentence that starts at the bottom of that page: Do Rajala and Laine state the smaller irregular particles of powders A and B did not show anisotropic behavior. -- carrying on to page 184 -- Only slight particles changes were visible over the temperature range where those powders lost moisture.

Did I read that correctly?

A. Yes, you did.
Q. And so these commercial samples of magnesium

stearate, even when put under cross polars never showed anisotropy regardless of what time or temperature they were held at; is that correct?

A. Yes. And if you recall, my demonstrative on anisotropy on the right-hand side, we had also the possibility of something that is not crystalline that doesn't exhibit anisotropy.

So these are commercial products that come from natural sources. So the quality of the crystal depends on who the supplier is.

Q. Now, Zydus's magnesium stearate sample is a commercial grade of magnesium stearate and magnesium palmitate, too; correct?

A. Correct.

Q. And am I correct that you do not request any visual method for thermal analysis to be conducted on that sample?

A. I did not request any visual method. I didn't request DSC either. I got information, and I was asked to determine whether the melting point of magnesium stearate in Zydus is below 90 degrees centigrade.

Q. Could you have requested a hot stage microscopy experiment be performed on Zydus's magnesium stearate sample?

A. Not after reviewing the literature. Because what I see is reports from three different laboratories in three different countries spanning over ten years, finding a

consistent property of the behavior of this material.

What I would -- if I request something would be for testing this particular lot, and this particular lot, I didn't request DSC because it came to me. I would have requested them immediately, but since the data was provided to me, I didn't have to make that request.

The loss of anisotropy is something that has been reported as I said in the different laboratories, different countries. So it is a property that reflects the behavior of this material. So I know, we know from that point of view what properties this material has.

Q. So am I correct, it is your opinion that DSC and TGA should be repeated on a batch by batch basis but hot stage microscopy does not need to be repeated on a batch by batch basis?

A. Well, actually, I was responsible for that when I was working in industry. And every batch, every single batch you have to conduct DSC and TGA.

The hot stage microscopy, we would use it when there were compounds that have never been seen. And then once the thermal behavior is understood, the hot stage microscopy becomes sort of like unnecessary because the differences can be pointed very precisely using instrumental methods.

Q. But when, for example, Miller and York and Rajala and

Laine studies magnesium stearate, that has been known for almost 100 years, is that correct?

A. Yes, and there were basically treating it as new material because this is a research article. This is research articles on magnesium stearate. So in that case, yes, there are studies of the property. And they actually, all of them found that there is a loss of anisotropy, which is a valuable contribution to the literature, because that means that scientists working with magnesium stearate know this fact.

Q. And am I also correct you did not request any hot stage microscopy to be performed on Zydus's magnesium stearate under cross polars?

A. I did not request hot stage of microscopy of any kind, including cross polars. We have information from the published literature. That is the objective and that is the use of the scientific literature.

Q. And am I correct that you have not seen a single test that tests the magnesium stearate sample by hot stage under cross polars?

A. No, I have not.

Q. So your opinion concerning anisotropy with respect to Zydus's magnesium stearate sample is derived solely from the literature; is that correct?

A. It is on the known behavior of magnesium stearate

from different studies conducted over years.

Q. You don't have any physical evidence on Zydus's magnesium stearate sample concerning anisotropy; correct?

A. No, I do not have on the Zydus material.

Q. Can you turn in your binder to PTX-496?

A. (Witness complies.)

Q. And am I correct, Dr. Pinal, that PTX-496 is an article called Thermal Analysis and Calorimetric Methods in the Characterization of Polymorphs and Solvates by Dr. Giron?

A. Correct.

Q. And you relied on that article in forming your opinions; is that correct?

A. Yes, I did.

Q. But you did not present this article during your opening testimony; is that correct?

A. No, I did not.

Q. If you could turn to Figure 12 on page 23 of Dr. Giron, also known at PTX-496.23.

A. Sorry. Which page?

Q. 496.23, or 23.

A. 23. Um-hmm.

Q. Am I correct that Dr. Giron here presents two exemplary DSC traces concerning a dehydration and a melt?

A. That is correct.

Q. And the first endotherm on each of these traces is

assigned to a dehydration' is that correct?

A. That is also correct.

Q. And the second endotherm is assigned to a melting of an anhydrous form; is that contract?

A. That is correct.

Q. And am I correct that Dr. Giron, on page 21, under pseudopolymorphism, refers to dehydration and melting events in a DSC such as this as type 1 desolvation or dehydration?

A. Sorry?

Q. Am I correct that Dr. Giron calls desolvation or dehydration that follows Figure 12 type 1 dehydration or desolvation?

A. Correct.

Q. Am I correct that Dr. Giron states that type 1 dehydration, desolvation occurs in the solid state?

A. Yes. And she also mentions, and I'm trying to look at it here, that the melt, the melting can occur during the dehydration and after dehydration. If you give me some time, we will find it because that is definitely stated in this paper.

Q. Why don't we look at these figures --

THE COURT: Can I just interrupt for a minute, please, Mr. Abramowitz?

MR. ABRAMOWITZ: Sure.

THE COURT: Out of curiosity, we have seen

discussion or graphs showing a dehydration or a melt previously what you variously argue about being a dehydration or a melt, and it shows the endotherm peak as a dip, not as an actual peak. Is there something about this scale why the melts and the dehydration are shown as actual peaks and not as an inverted peak? If you understand what I'm asking, Dr. Pinal.

THE WITNESS: Your Honor, so you mean the direction of the peak?

THE COURT: That's it exactly.

THE WITNESS: Yes, sorry. This has to do with the manufacturer of the instrument. And for some reason, you know, say, one brand will choose to show endotherms pointing down and some other maker would choose endotherms pointing up. So in the literature -- well, it doesn't indicate. Oh, yes. If we go up to Figure 10, for example, of this, that will illustrate how this was reported.

THE COURT: That's okay.

THE WITNESS: What they do is when you see a DSC plot, a good practice is not here on every, on every one, but on some is, is to put an arrow pointing and say either endo or exo, so the reader can tell what type of instrument was used.

THE COURT: Good enough. Thanks. Thanks. Sorry.

MR. ABRAMOWITZ: Of course, Your Honor. And that actually clears up a slide I'm about to use. So that helps.

BY MR. ABRAMOWITZ:

Q. Dr. Pinal, if you go to Figure 13 on page 24 of Giron.

And am I correct here in Figure 13, Dr. Giron describes what is first a melt occurring with dehydration, and then a recrystallization to an anhydrous form, and then the melting of the anhydrous form?

A. That is correct. And here, for example, we can see because this figure has all the attributes of magnesium stearate, but it shows it more clearly than on the wide broad peak that we saw with Dr. Hanton's analysis.

Here, under the fusion, is another term for melting. Some people call it fusion, some people call it melting and loss of water which is another word for dehydration.

What we see here is dehydration and melting taking place at the same time.

Now, this is the recrystallization, which is the liquid going to the anhydrous form. And from one of the questions that I got from Mr. Lief, he asked me why is it that we don't see that negative peak in there? And that my answer was that it was buried under this first peak.

So now, what we can see here is that these two peaks are not really separated. They overlap. And any analytical chemist would tell you this. The only way you can tell if two peaks are resolved is whether there is baseline to baseline separation. So the only way we could say that these two peaks are not overlapping is if there was one peak and then baseline and then the other peak.

In this particular case, we see a shoulder. So this indicates that the recrystallization overlaps with the dehydration and melt, precisely the same thing. If, for some reason, these material happen to crystallize a little bit faster, this peak would be shifted to the left, and it will be buried under the first endotherm. And the net result is that these endotherms would look wider and a little bit smaller in height.

So this is precisely the type of situation that we have. But in this illustrative case, is very good for teaching purposes because it shows that it is just a partial overlap. It is not complete overlap.

Q. Dr. Pinal, just to sum up. Am I correct that Dr. Hanton's DSC does not show an exotherm?

A. Yes, you are correct. The exotherm is buried under the endotherm, and the result is a wide endotherm, net endothermic peak.

Q. And am I correct that Dr. Giron on page 21 refers

to this type of desolvation or dehydration as a type 2 desolvation and dehydration?

A. Yes, and that is what I was looking for. Because in that one, she refers to that, she mentions the melting can take place during the dehydration or after dehydration. And in this particular case, we see that -- sorry -- the recrystallization is happening. Well, melt, you know -- let me take that back.

That melting can take place during dehydration or after dehydration, and the recrystallization can take place during the process or right after, as illustrated in this case.

MR. ABRAMOWITZ: Dylan, do you have the Giron cross, please?

BY MR. ABRAMOWITZ:

Q. Dr. Pinal, do you see I have taken Dr. Hanton's DSC and made the endotherms go up on this slide?

A. Correct.

Q. Looking visually at these pictures, Dr. Pinal, can we play a game they play on Sesame Street? Which of these figures does not look like the others?

A. Well, that is where the interpretation of the DSC comes into play, because one of the things to note here, as I mentioned, this peak, the second, the second endotherm, 125 degrees for the Zydus magnesium stearate, is very sharp

and narrow, and the molecules, all the molecules on the second peak are the same molecules as they were present during the first transformation.

If you want to get a melting peak, these beautiful. What I mean to say, if you want to get a melting peak that is this sharp and narrow, what you need to do is to obtain the molecules in the liquid form because only from the liquid form they can align themselves and to give you these in this high of, this kind of high purity.

And, Your Honor, here, what I mean by purity is physical purity, physical perfection of the crystal. That is what we see here.

So if we start looking at the shapes, there is not necessarily what is the shape. The part of the analysis is to read what is the relationship between the different transitions because in the end, the second endotherm which we see on the Zydus product is that final product from the first transformation.

Q. And just one more question on Giron, Dr. Pinal. Am I correct that mesophases can provide sharp melting peaks?

A. Mesophases can provide sharp melting peaks, but one of the things to look at is what is the amount of energy involved.

So the area under the peak is a measure of the energy that took to break those, those interactions.

So this is, you know, the first one is about 100 joules per gram, the other is about 40 joules per gram. So the reason you would get very sharp peaks on the mesophase melting is because interactions are weaker so it will be very sharp because it will be, it would take less energy.

MR. ABRAMOWITZ: Your Honor, we would like to move in Figures 12 and 13 of PTX-496.

MR. LIEF: No objection.

THE COURT: They're admitted without objection again.

(Figures 12 and 13 of PTX-496 are admitted into evidence.)

THE COURT: Just assume you all understand that I expect to see that on a different exhibit. Right? And when you do that, please, obviously include the source of it so I know where it was.

MR. ABRAMOWITZ: Understood, Your Honor.

BY MR. ABRAMOWITZ:

Q. Dr. Pinal, can we turn back to PTX-499, the Ertel and Carstensen article?

A. Yes.

Q. If we turn to page 176 which is PTX-499.7.

A. Um-hmm.

Q. Starting at the paragraph that starts the structural differences.

Am I correct that Ertel and Carstensen report: The structural differences between the 3 hydrates alluded to earlier were confirmed by x-ray powder diffraction using randomly oriented samples (Figure 10). Of particular interest is the region near 2 theta equals 21 degrees. The diffractogram of the dihydrate exhibited several distinct peaks in this region, while in the case of the anhydrate, these peaks were replaced by a single broad peak. This type of peak is known as a halo, and is indicative of a structure that in which the magnesium atoms of magnesium stearate are arranged in irregular spaced particle planes, i.e., the three-dimensional crystal lattice has been disrupted (Vold, 1949).

Did I read that correctly?

A. Correct.

Q. And you testified earlier about the disruption of the three-dimensional structure during the first endotherm; is that correct?

A. Correct.

Q. Am I correct that you did not rely on Vold 1949 to offer your opinions?

A. No, I did not.

Q. Can we turn to DTX-2009, Vold 1949.

A. I'm sorry. Which number is it?

Q. DTX-2009.

A. Oh, sorry. Yes. I know this by Hattiangdi.
Q. Actually, I think the Hattiangdi is the next article in this journal.
A. Oh, yes. Because this is one of the articles that I, general articles I have consulted.
Q. If you look at page 2320, I think that is the first page of the article that you relied on, the Hattiangdi article; is that correct?
A. 2320. Okay.
Q. And that's the Hattiangdi article: Differential Thermal Analysis of Metal Soaps; is that correct?
A. That's correct.
Q. So going back to the Vold article, if we could.
A. I'm sorry. Um-hmm.
Q. If we could look on page 2318, in the right column, in the paragraph starting "drying."
A. Sorry. In which paragraph?
Q. Vold and Hattiangdi state, on page 2318 in the right column: "Drying" of magnesium palmitate and stearate at 90 degrees C results in a form in which the long spacing is substantially decreased and the numerous short spacings original present are replaced by a single intense peak at 4.18 degrees angstrom -- or 4.18 angstroms. (Figure 2). The originally crystalline soap has, therefore, been converted into a liquid crystalline or mesomorphic form in

which the heads of the molecules are still in regular planes (intense, sharp, long spacing) but the lateral arrangement has been lost except for an average distance of separation of planes corresponding to hexagonal close packing. That this change was not due to thermal transition was shown by preparing another sample which was not heated to high temperatures and was dried at room temperature under vacuum at P_2O_5 but nevertheless gave the same direction pattern of the sample dried at 90 degrees C. The water loss from these soaps was substantial. So there is considerable likelihood of the existence of a hydrate, although the present data are insufficient to establish it.

Did I read that correctly?

A. Yes, you did.

Q. Am I correct here, Vold and Hattiangdi are discussing the dehydration of magnesium stearate?

A. Yes.

Q. If we turn to Figure 2 on page 2317, do you see in the lower box some x-ray powder diffraction analysis of magnesium stearate and magnesium palmitate?

A. Yes.

Q. Okay. And it looks at the magnesium stearate and magnesium palmitate being air dried, dried at 90 degrees C, or cooled slowly from 200 degrees C. Do you see that?

A. Yes.

Q. Am I correct there are sharp peaks in the air dried samples in Figure 12?

A. Yes.

Q. And am I correct that sharp peaks on an x-ray powder diffractogram indicate a solid substance?

A. Yes. Because in order to even test the sample, you have to wait until whatever changes are going to take place finishes taking place, and then you take the solid and put it in the instrument.

Q. And am I correct that for the substance dried at 90 degrees C, there are sharp peaks on the x-ray powder diffractogram?

A. Yes.

Q. And am I correct that these sharp peaks indicate that the substance dried at 90 degrees C wasn't solid?

A. Since the melting point of magnesium stearate, magnesium palmitate is lower than 90 degrees C, is similar to what we discuss regarding Miller and York. They placed the sample in a chamber of 90 degrees C, and then they let it happen, whatever was going to happen, and after some time, they pull it out. So the transformation that took place going to the liquid have already taken place by the time we are looking at these data.

So what we are doing, what we are looking at here is the x-ray diffraction of the crystalline substance

which is the final product from the transformation of the hydrated form that was the original substance, similar to what happens with the Zydus magnesium stearate.

Q. Now, am I -- going back to page 2318. Dr. Pinal, do you understand what the anisotropy and isotropic of a hexagonal phase of a molecule are?

A. Well, if they are anisotropic, it means that they have different, they have different directions -- different properties in different directions. And if they are isotropic, that means that the properties are the same in different direction.

Q. What are the properties for hexagonal phase?

A. That I couldn't tell you off the top of my head, but one of the things that is common to all anisotropic materials is that they will actually produce a secondary rate that can be observed of the cross polars. And as we discussed earlier, the only way in which you could maybe not see it is if you have every single molecule, part of the same grain, which for magnesium stearate nobody has been able to achieve.

Q. And just, finally, so the record is clear, am I correct that a solid can transform into a mesophase or liquid crystal without first going through an isotropic liquid state?

A. A solid can convert into a mesophase or a liquid

phase -- or, sorry, let me take that back.

A solid can convert into a mesophase or into a liquid crystalline phase. And on what the difference would be between going to that change or going into a liquid is that there would be anisotropy at all times. Because you go from one structure that is orderly to another one that is orderly directly. So you would need to have, you would need to see anisotropy at all times. Otherwise, if you lose anisotropy, you went through a random distribution of the molecules. Again, that is the principle of a liquid.

So what you said, yes, it is possible, but the condition that would actually show it would be to have anisotropy at all times.

Q. Now, am I correct that Ertel and Carstensen, Miller and York, and Rajala and Laine all conducted hot stage microscopy?

A. Yes.

Q. Am I correct that not a single one of them reported that after the loss of anisotropy, anisotropy was regained upon recrystallization?

A. No. But one of the things that they indicated, there is a melting. So as part of this scope of the discussion, they actually attribute the second peak to a melting, which indeed it is a melting but it is a melting of the anhydrous form.

The fact that they recognize that as a crystal form is, there is no need to indicate there is anisotropy. Because if the crystal is melting, the crystal is anisotropic so it will be redundant.

The surprising fact that they actually capture in their summary was the fact that as they were hitting through that dehydration, the anisotropy was lost and that is why it was, it was, I can say it was surprising to them because it is only five lines and they use only one line, so 20 percent of the summary to indicate that point to the literature.

So that was the point because if they show that they increase salt before 125 degrees and they do the cross polar, it would be redundant. And likely, you know, bear with me for one second because it is a good chance that even the editor will ask them to remove it because what is the point of showing the anisotropic property on the material that is not to be a crystal because there is a subsequent manner.

Q. Doctor, you have no evidence that any reviewer asked them to remove?

A. You are right, and I apologize for that. But the point, there is a fact, is that the effect of the loss of anisotropy is roughly 20 percent of their summary. So more people read a summary than read entire paper, and that is

the fact that is of greatest significance.

And what I can tell you as a scientist that works in this area, that if you know you have a crystal, there is no need to show that it is a crystal by showing anisotropy. That would be redundant.

Q. And one final question, Dr. Pinal. Am I correct you do not request any XRPD studies be done of magnesium stearate samples while it was heated?

A. No, because XRPD is x-ray powder diffraction. It is, the purpose of that is to determine crystalline structure for solids. I was asked to determine whether the melting point of magnesium stearate and the melting point of magnesium palmitate in the Zydus product are lower than 90 degrees centigrade, and all the information that I have reviewed support my conclusion that indeed the melting points of both magnesium stearate and magnesium palmitate present in the Zydus product are lower than 90 degrees centigrade.

Q. Am I correct you did not request a modulated DSC be conducted on Zydus's magnesium stearate sample?

A. I did not request a modulated DSC.

Q. Am I correct that variable temperature XRPD and modulated DSC are techniques that could have provided information as to whether Zydus's sample reaches the liquid state during the dehydration phase?

A. Regardless the modulated DSC, modulated DSC is using the same instrument of the DSC. You use a heating ramp going in a straight line. It's going up and down. It is designed to separate overlapping events. And in principle, that is the type of instrument that would separate facilitating overlapping events. And if you go to the literature today, you would find about 1,200 references on that subject. But one of the things that it has is it has some very particular situations where it actually really works well. So the fact of, you need if you know what type of event you have because then you can actually give you a better idea, but in some occasions it doesn't work.

In this particular case, with a DSC, what we can see is that we have a broad endothermic peak followed by a sharp and narrow endothermic peak, involving the exact same molecules. And that relationship is missed many times, people who don't work on a daily basis with DSC.

However, that is a very clear indication of what is what happen, and that tells us that the type of crystalline, the second transition, is of high physical quality and the type of crystal that can only be produced from a liquid, and the information from the literature showing there is a loss of anisotropic property indicating the presence of a liquid is coming together.

So is just taking all the parts, and all of them

is a coherent story of what is happening.

Q. This is a yes-or-no question, Dr. Pinal. You just said modulated DSC can separate that out, but you did not ask that to be required?

A. I did not ask. It was not necessary.

MR. ABRAMOWITZ: No further questions.

THE COURT: All right. Thank you, Mr. Abramowitz.

Any redirect?

MR. LIEF: Nothing on redirect.

THE COURT: All right. Thank you, Doctor. You may step down.

THE WITNESS: Thank you, Your Honor.

THE COURT: Your next witness, Mr. Haug.

MR. LIEF: Next, we will call Dr. Sinko who will opine on infringement.

THE COURT: All right.

MR. LIEF: May I approach with the books?

THE COURT: Why don't we take a short break; all right? We'll take ten minutes, ten to 12. We'll be back at 20 to. Okay?

(Brief recess taken.)

* * *

(Proceedings reconvened after recess.)

THE COURT: Thank you. Please be seated.

Mr. Lief, the next witness.

MR. LIEF: The next witness will be Dr. Patrick Sinko who will opine on infringement.

THE COURT: All right. Thank you.

... PATRICK JOHN SINKO, having been first duly sworn, was examined and testified as follows ...

THE COURT: Thank you. You may be seated.

MR. LIEF: If we might approach the witness with a binder.

THE COURT: Yes, certainly.

(Binders passed forward.)

THE COURT: And you may proceed, Mr. Lief.

DIRECT EXAMINATION

BY MR. LIEF:

Q. Good morning, Dr. Sinko.

A. Good morning.

Q. What is your profession?

A. I'm a pharmacist and a pharmaceutical scientist.

Q. All right. And I'd like to take a look the PTX-840. And can you tell me what this is?

A. This is a copy of my CV.

Q. And is the information reported in this CV accurate and up-to-date?

A. I think this version is as of June 2014, so there have been some additions to publications and appointments

and grants and things like that, but it is mostly correct and up-to-date.

MR. LIEF: All right. We would move PTX-840 into evidence.

MR. PETERKA: No objection, Your Honor.

THE COURT: It is admitted without objection.

(PTX-840 is admitted into evidence.)

BY MR. LIEF:

Q. Can you briefly describe your educational background?

A. Sure. I'm a pharmacist having graduated in 1982 from College of Pharmacy at Rutgers University. And I also, I received my Bachelor of Science Degree in Pharmacy.

I received my Ph.D. in Pharmaceutics from the University of Michigan - College of Pharmacy in 1988.

Q. If we could take a look at Plaintiffs' Demonstrative Exhibit 8.1. Can you tell me what is shown here?

A. This is a summary slide of just some highlights from my CV. And I just discussed my educational background in the upper left. And this is just a select listing of some of the appointments and experience, awards and honors, publications, and some of my duties as a peer reviewer and as an editor.

As you can see, in my appointments and experience, I have been an editor and also been on the Board of Scientific Advisors, Controlled Release Society, which is

a society focused on controlled release dosage forms. That was an elected position.

I have also received numerous awards in my career, probably the most significant of which is the MERIT Award from the National Institute of Health which is given to less than one percent of the grantees for innovative research.

I also have published extensively and been very active in research, having about 450 publications in total, with about 170 primary papers.

One thing about publishing and getting grants the way we do is they always ask you to then peer review grants and papers, so I have extensive experience as a peer reviewer both for journals in our field, such as the Journal of Controlled Release, about 50 journals in all over my career.

And I have been extensively involved as a grant reviewer for various international and national organizations such as the National Institute of Health.

Q. In terms of your work as a peer reviewer or a grant reviewer, can you describe for us a little bit of what that entails?

A. Sure. So as a reviewer in general, be it for a paper or a grant, the person submitting the document will submit an experimental design and a plan and methods how to control

for the study the data they generate, how they analyze and how they interpret the data. And I routinely am called upon in a variety of modes, as you can see from that one bottom right corner of the slide, to do this on a regular basis and review others data and make sure that the interpretation is scientifically sound.

Q. All right. I take it you are currently employed, Dr. Sinko?

A. Yes, I am.

Q. And where are you currently employed?

A. I am employed by Rutgers University where I am a Distinguished Professor of Pharmaceutics and the Parke-Davis Chair Professor in Pharmaceutics and Drug Delivery.

I also have appointments in the School of Engineering, the Department of Biomedical Engineering, and Chemical Biological Engineering, as well as Pharmacology and Toxicology.

Q. Can you describe for us a little what you do as a Professor, as a Distinguished Professor at Rutgers?

A. Well, as a Professor, I'm still expected to do the three basic components, which are research, teaching, and service. I have a very active research lab and enter a normal complement of graduate students and undergraduate students in my research.

My teaching still occurs at the graduate level,

occasionally at the undergraduate level. But because I'm also an Associate Vice President in the Office of Research and Economic Development, my teaching duties have been scaled back.

Q. What kind of courses do you teach and have you taught in the past?

A. Well, I have literally taught every single course in the pharmaceutics sequence at the professional undergraduate level, and I taught in many courses leading -- I'm still leading advanced physical pharmacy and pharmaceutics courses at the graduate level at this point in time.

Q. Have you been accepted as an expert in pharmaceutical science in Federal Court previously?

A. Yes, I have. I've been accepted as an expert in pharmaceutical science and formulation three times in the Southern District of Florida. In fact, two times as it relates to litigation to the '720 patent as well as one time in the Eastern District of Texas.

MR. LIEF: At this point, Shire would offer Dr. Sinko as an expert witness in the field of pharmaceutical science and formulation.

MR. PETERKA: No objection.

THE COURT: All right. He is admitted as an expert. Thanks.

BY MR. LIEF:

Q. Dr. Sinko, what have you been asked to do with respect to this case?

A. I've been asked to assess if Zydus's ANDA product infringes on claims 1 and 3 of the '720 patent.

Q. Have you formed an opinion with respect to those questions?

A. Yes, I have. And it is my opinion that the Zydus ANDA product does infringe claims 1 and 3.

Q. If we could take a look at PDX, Plaintiffs' Demonstrative Exhibit 8.2. What is this?

A. Well, this is a demonstrative I prepared to show the basis for my opinion. And as you can see, I relied upon the '720 patent, the Court's claim construction as well as Zydus's ANDA where they describe the formulation and the manufacturing process, Zydus's formulation development records for the different formulations, scientific literature as well as the Zydus formulator testimony, as we heard yesterday from Mr. Kulkarni, as well as testing and opinions from Shire's experts that we have seen over the past couple days.

Q. All right. I'd like to take a look at PDX-8.18. And I'll ask you, have you compared the elements of these claims, claim 1 and claim 3 with the accused product from Zydus?

A. Yes, I have.

Q. Based upon the evidence that you have seen, does the Zydus ANDA product contain 5-amino-salicylic acid?
A. Yes, it does.
Q. And is that also known as mesalamine?
A. Yes, it is.
Q. Is the mesalamine in the Zydus ANDA product present in an amount from 80 to 95 percent of the total composition?
A. Yes, it is.
Q. And is the Zydus product an oral pharmaceutical composition?
A. Yes, it is. It's a tablet.
Q. If we could take a look at Plaintiffs' Trial Exhibit 844. I would begin by asking you what is this document?
A. So this is the complete response amendment for the resubmission of Zydus's ANDA.
Q. And if we could take a look at page 844.7.
Can you tell us what is shown here?
A. So this is a table of the processes, summary of the processes and ingredients and their amounts for the Zydus exhibit batch EMM196.
MR. LIEF: We would move PTX-844 into evidence.
MR. PETERKA: No objection.
THE COURT: Admitted without objection.
(PTX-844 is admitted into evidence.)

BY MR. LIEF:

Q. Now, is the Zydus product a controlled release oral pharmaceutical composition?

A. Yes, it is.

Q. And when we say "controlled release," what does that mean?

A. Well, I described "controlled release" the same way that Dr. Little did yesterday. It's not basically immediate release. It's where you can get 70 percent released in up to 45 minutes.

Q. If we could take a look at Plaintiffs' Trial Exhibit 208, which I believe has already been admitted.

What is this document?

A. This is part of the Zydus ANDA. This is the quality overall summary.

Q. Now, this quality overall summary, does it apply to the resubmitted batch EMM196?

A. Yes, under that understanding, and we heard that yesterday in Mr. Kulkarni's deposition played.

Q. All right. If we could turn to page 208.21. It's towards the bottom there.

What is stated there with respect to controlled release?

A. So this shows the motivation of Zydus. If you look at that second part, second line. Their product was

designed to have a similar release profile through the inclusion of both DR and ER components in each tablet.

And they defined DR and ER above, which are delayed release and extended release. And those two components make up the controlled release.

MR. LIEF: I think we have done it, but to the extent we didn't, we would move PTX-208 into evidence.

MR. PETERKA: No objection.

THE COURT: It is admitted.

(PTX-208 is admitted into evidence.)

BY MR. LIEF:

Q. I'd like to turn to PTX-626.

Do you recognize this document?

A. Yes. This is a letter from Zydus to the FDA on the resubmission of their ANDA product. It is the complete response amendment.

Q. And I'd like to turn to page 626.12, and in particular focus on the left-hand side graph.

What does this graph show?

A. This is a release profile of the batch EMM196, although it is terrible copy. And what it shows, if you look at that one hour time point, and just a little bit before that at 45 minutes, it only shows about 10 percent released. So this confirms that Zydus's product is a controlled release product.

MR. LIEF: We would move Plaintiffs' Trial Exhibit 626 into evidence.

MR. PETERKA: No objection.

THE COURT: It is admitted without objection.

(PTX-626 is admitted into evidence.)

BY MR. LIEF:

Q. And, Dr. Sinko, were you present for Dr. Little's testimony?

A. Yes, I was.

Q. Do you agree with his opinion that the Zydus product has a controlled release profile?

A. Yes, I do. And I think you also saw from Ms. Gray's testing, Dr. Little's report that they showed that after the delayed release coating had come off the tablet in about three hour time period, you saw the sustained or extended release of mesalamine of a little bit over a four hour period. So that would be a controlled release product. So I do agree.

Q. What to you attribute the controlled release of Zydus's product to?

A. Well, I attribute the controlled release behavior that is observed to the two matrices present in the product, and I guess we'll be getting to that in a bit.

Q. To change topics a little bit, I'd like to discuss the Zydus manufacturing process. Are you familiar with that?

A. Yes, I am. I reviewed the ANDA documents.
Q. And what did you learn from your review of Zydus's manufacturing processes?
A. Well, my review of Zydus's documents related to the process show the amount, I'm sorry, the excipients, the active ingredient, all those ingredients, their amounts, the processing steps, and basically what it shows is not only what the ingredients are but where they end up in the final Zydus ANDA product.
Q. All right. If we can again turn to 844.7. DTX-844.
There is a heading there that says Compaction. What is that related to?
A. So, once again, this is for the exhibit batch EMM196. And compaction occurs after they mix those three ingredients -- mesalamine, colloidal silicon dioxide, and magnesium stearate. And compaction here is referring to the first granulation step. It's a dry granulation method that is used at this step.
Q. And what is produced as a result of that dry granulation method?
A. Well, what is produced in this step is, of course, the granules and fines as well.
Q. Okay. What are fines?
A. Fines are small particles of the ingredients such as mesalamine.

Q. In a general sense, before we get to the specific second step that is labeled granulation, can you describe for us what granulation is?

A. Sure. So granulation, typically you are dealing with powders. And to make them so they're more processable during the manufacturing process, you bring these powders together in a variety of ways, dry or wet granulation, to make larger particles. And we call them granules as well.

Q. So then, below the compaction step, there is an actual step that is entitled granulation. Can you tell us what is going on in that step?

A. Sure. At this step, this is actually the other type of granulation. So the first step was the dry granulation. This is now a wet granulation. And this is where you take the particles and fines from the first step, you mix them with the hydrophilic excipients, carboxymethylcellulose sodium and sodium starch glycolate, and you then make a light granulation using that carboxymethylcellulose and sodium starch glycolate solution.

Q. And after the two granulations are completed, what happens next?

A. Well, you take those materials. As you can see, there is a lubrication step where you take the materials in the lubrication step and you mix them thoroughly. You compress them into tablets, and then you apply two coatings.

One is a delayed release coating and the second is the film coating.

Q. If we can turn back to PTX-208. In this instance, I'd like you to look at PTX-208.37.

Can you tell us what this is?

A. So this is a more detailed description of the process, and now it's giving you a more granular level using a flowchart. You can see down on the left once again the same excipients as in the -- sorry -- same ingredients as in the prior demonstrative slide.

And just so, for example, they take the colloidal silicon dioxide and magnesium stearate. And after adding the mesalamine, they sift it. They then blend it in an egg shell blender, so this makes a homogeneous mixture. It then goes into the first granulation step, the compaction step that I just described.

Once those granules are made and sized, they then are mixed with the hydrophilic excipients once again, and after thorough mixing, they are now wet granulated, as I described previously. They are then dried and sized.

And I think it continues on the next. Sorry. Just go back up a little bit.

And then after it is dry and sized, they're adding the lubrication ingredients and then compacted into tablets after blending once again.

And then you go through the other coating steps.

Q. If we could now turn to PTX-287.

In looking at this, what is this document?

A. And so this is batch manufacturing record for EMM196, as you can see up on the top there, for the mesalamine -- for the mesalamine tablets that Zydus makes.

Q. What kind of information does the batch manufacturing record supply?

A. The batch manufacturing record supplies all of the details from the amounts and processing time, how to run the machines, a lot of the details that the flowchart and other tables left out. This is a very exacting standard operating procedure type document.

MR. LIEF: All right. To the extent we don't have it in evidence, we would move PTX-287 into evidence.

MR. PETERKA: No objection, Your Honor.

THE COURT: Admitted without objection.

(PTX-287 is admitted into evidence.)

BY MR. LIEF:

Q. Dr. Sinko, have you prepared a summary of Zydus's manufacturing processes?

A. Yes, I have.

Q. Take a look at PDX-8.3.

Can you describe what this is?

A. Sure. So I tried to prepare a demonstrative that

gave an overview of the variety of documents that we just reviewed. And as you can see here, in the first step, you are taking the active ingredient, mesalamine, the colloidal silicon dioxide, the magnesium stearate, and then using that compaction dry granulation step, you make the first granulation. And this is where the magnesium stearate is added to that inner granule and locked into place.

They are then sized, and as a result of that sizing process, you do make those granules. And because of the nature of the sizing process, you also have these fine particles. These are mixed with the hydrophilic excipients, CMC and SSG, wet granulated as I described prior to making the larger granules or particles. They are then sized once again.

And what you can see in the far left is a depiction of what these granules look like. So you can see there is the first granulation from that dry granulation step, and in some cases you see the hydrophilic materials surrounding a single particle. You also see the hydrophilic materials surrounding aggregates of particles.

This is exactly what granulation was supposed to do is to bring particles together and, of course, the ultimate size in the end depends on the sizing process.

THE COURT: You say, you have used the word "sizing" a couple of times, Dr. Sinko. It does not appear

on your chart there, this demonstrative. What does that mean and what does it correspond to, if anything, on the chart, on the demonstrative?

THE WITNESS: Yes, absolutely. The sizing and milling are used synonymously.

THE COURT: They're synonymous.

THE WITNESS: Yes. Sometimes they're referred to as milling and sizing. The milling would produce a size particle, and then there is some sort of screen that would then let those, the properly sized particles pass through.

THE COURT: Okay. Thank you.

THE WITNESS: And then once you make the second granulation, you would go to the blending and lubrication steps, compress a tablet and then coat them.

BY MR. LIEF:

Q. All right. If we could turn to claim element 1(a). I'd like to look at PDX-8.4 and ask you what is this?

A. So this is my understanding of the construction of several terms for claim 1(a). The two terms that were agreed upon were for "matrix," and "lipophilic."

"Matrix" being "a macroscopically homogeneous structure in all its volume."

And "lipophilic," "poor affinity towards aqueous fluids."

The Court then construed "inner lipophilic

matrix" as "a matrix that exhibits lipophilic properties and is separate from the outer hydrophilic matrix."

Q. Have you applied these claim constructions in forming your opinion?

A. Yes.

Q. Have you formed an opinion as to whether Zydus's product has an inner lipophilic matrix?

A. Yes, it is my opinion that Zydus's product has an inner lipophilic matrix.

Q. Where is the inner lipophilic matrix in the Zydus product located?

A. It's inside the granules that are made in that first compaction step.

Q. All right. Is magnesium stearate in those inner granules?

A. Yes, it is. You saw from the manufacturing process, it is directly put into the granules.

Q. Is magnesium stearate a lipophilic substance?

A. Yes, it is a potent lipophilic substance.

Q. Is magnesium stearate the salt of a hydrogenated fatty acid?

A. Yes, it is.

Q. Is magnesium palmitate in those inner granules?

A. Yes, it is. Actually, as we just saw from Dr. Pinal's testimony, there is magnesium palmitate in

commercial grade magnesium stearate.

Q. And is magnesium palmitate a lipophilic substance?

A. Yes, it is.

Q. Is magnesium palmitate the salt of a hydrogenated fatty acid?

A. Yes, it is.

Q. Do the ingredients in that inner region of that granule that result from roller compaction, do they form a macroscopically homogeneous structure in all its volume?

A. Yes, it does.

Q. And does Zydus's magnesium stearate, in the inner granule, form a macroscopically homogeneous structure in all its volume?

A. Yes, it does.

Q. And what is your basis for those conclusions?

A. Well, my basis for those conclusions is Zydus's testing as well as their processing systems.

Q. Right. If we could take a look at PTX-287, the batch manufacturing record again at page .39. And I would focus you in on steps 5.1.2 and 5.1.5.

Can you tell us how, if at all, this informs your opinion?

A. Yes. So, once again, this is for the exhibit batch EMM196. And this is, if you look at 5.1, this is the preparation of the premix. And so this is where they add

the colloidal silicon dioxide, magnesium stearate. Down at 5.1.5, you can see they add the mesalamine and they're thoroughly mixed in an egg shell blender causing or resulting in the homogeneous mixture of those ingredients.

Q. All right. If we can go forward to page 287.44. And I'd like to focus you in on steps 6.3.1, 6.3.4, and 6.3.5.

Can you tell us again what is happening here?

A. So at this point, the blend of the three ingredients has been performed. And they're now taking that blend and roller compacting to make the first granulation.

And so what you see in 6.3.1 is they take the material from the prior step. They're then going to put it through the granulator and/or the compactor.

And as you can see in 6.3.4, they're then sized after they're being made. And this is what I was describing before, it is that the .8 millimeter screen, so the granules are the correct size and the fine particles would pass through that.

And then in 6.3.5, you can see they collect the granules for the next processing step.

Q. We discussed this a little bit already, but how do you know the granules are formed?

A. Well, the roll compaction is an established method for dry granulation. But if you also look at it right here in their own records, Zydus is stating that they're

collecting granules.

MR. LIEF: Your Honor, we're about to start something of a new subject matter. I know, I think you said 12:15.

THE COURT: That's true. But you know what let's go ahead and take our last five minutes.

MR. LIEF: That's fine.

BY MR. LIEF:

Q. All right. I'd now like to turn to PDX-8.4.

Can you tell me what this is?

A. So this is a demonstrative that I prepared to discuss the "inner lipophilic matrix" terms, the two agreed upon terms in this claim 1(a) element. Once again, our "matrix" in the lipophilic matrix being "macroscopically homogeneous structure in all its volume" and "lipophilic" being "poor affinity towards aqueous fluids.

The Court construed "inner lipophilic matrix" to be "a matrix that exhibits lipophilic properties and is separate from the outer hydrophilic matrix."

Q. With regard to the construction regarding lipophilic properties, have you formed an opinion as to whether Zydus's inner lipophilic matrix -- let's just say Zydus's inner matrix exhibits lipophilic properties?

A. Yes, it's my opinion that Zydus's product forms an inner matrix with lipophilic properties.

Q. If we look at PDX-8.5.

Can you tell me what this is?

A. Well, this is a summary of the basis for my opinion. The literature has shown that magnesium stearate is a known potent lipophilic substance, and that it can impart lipophilic properties on blends.

I have also relied upon Zydus's formula development documents as well as the testing that Dr. Hoag described yesterday.

Q. All right. If we could turn to Plaintiffs' Demonstrative Exhibit 8.6.

Can you tell us what this is?

A. Sure. This is a demonstrative I prepared to show where in the '720 patent the lipophilic properties are described.

And there are two passages up here that I highlight. One is from the background of the invention where it states: 1. The use of inert matrices, in which the main component opposes some resistance to the penetration of the solvent, due to the poor affinity towards aqueous fluids; such property being known as lipophilia.

And this is from the '720 patent, column 1, lines 17 through 20. And this is basically where they define the word "lipophilic."

And then in the detailed disclosure of the

invention, they state: ... until the further penetration of the water would cause the disintegration of the hydrophilic layer and therefore the release of the content which, consisting of lipophilic granules, however induces the diffusional mechanism typical of these structures and therefore further slows down the dissolution profile of the active ingredient.

And this is once again from the '720 patent, column 3, line 66 spanning to column 4, line 5.

And, once again, this describes the behavior of lipophilic properties.

Q. Turning to magnesium stearate. I'd like to turn to PTX-852.8.

Can you tell us what this is?

A. Sure. This is a copy -- I'm sorry -- this is an entry from the Handbook of Pharmaceutical Excipients for magnesium stearate.

Q. And if we look at PTX-852, page .9 in section 19.

Can you read into the record the beginning of that?

A. Sure. The first sentence of section 19 reads: Magnesium stearate is hydrophobic and may retard the dissolution of a drug from a solid dosage form.

THE COURT: Okay. I think we're ready. We're at the magic hour.

With that cliffhanger, we'll go ahead and take our break. I'll see you all back here at 1:45. Okay? Thanks very much.

(Brief recess taken.)

* * *

Afternoon Session, 1:45 p.m.

THE COURT: Good afternoon. Thank you.

Please take the stand, Dr. Sinko. Of course, you remain under oath.

Please proceed, Mr. Lief.

MR. LIEF: All right.

BY MR. LIEF:

Q. Good afternoon, Dr. Sinko.

A. Good afternoon.

Q. I'd like to turn to another exhibit, PTX-629. And I will ask you: What is this?

A. This is a paper published in the European Journal of Pharmaceutics and biopharmaceutics by Uchimoto and colleagues that examine the comparative study of glycerin fatty ester and magnesium stearate on the dissolution of acetaminophen tablets using the analysis of available surface area.

Q. All right. And if we could turn to PTX-629.3. There's a graph, Figure 1A there and a caption below it. And can you explain what these results show?

A. So in panel 1A, as you can see in the caption, this is where they vary the amount of magnesium stearate, and they varied it from 0.1 percent to concentrations of three percent, and you can see where this is now a dissolution plot.

First is time. Then you can see that at color, all colored lines are the concentrations below three percent that significantly slow the dissolution of the drug whereas the lowest .1 percent, it does not. So this shows that magnesium stearate at low concentrations can significantly slow drug release.

Q. Now, how does magnesium stearate slow drug release?

A. Well, the only way that I know that magnesium stearate can slow drug release is by imparting a lipophilic character to the area where the drug is. And that lipophilic property or character is that it repels fluid. So by controlling the penetration of fluid or water to mesalamine, you control its dissolution, which means you then control its release.

Q. Does the magnesium stearate in the inner region of the Zydus granules slow release of drug?

A. Yes, it does.

Q. And what do you base that conclusion on?

A. Well, I've seen some Zydus test formulations and I base my conclusion on those results.

Q. All right. If we could take a look at -- well, before I do that, with respect to PTX-629, the Uchimoto article, we would move Figure 1A and its caption be admitted.

MR. PETERKA: No objection.

THE COURT: All right. It's admitted without objection.

(PTX-629 was admitted into evidence.)

BY MR. LIEF:

Q. All right. Now, if we could turn to PTX-288. And what is this?

A. This is a laboratory notebook, a Zydus lab notebook. As you can see on the top, it says LNB/MESDRY/203, and this is from one of the test formulations that we'll be describing.

Q. All right. And if we could turn to PTX-288.46. Can you tell me what is shown on this page?

A. Sure. So this is the, one of the pages in the laboratory notebooks. This test formulation was designated F108. And if you look at the objective, it's to make a batch of mesalamine tablets using a wet granulation technique. And if you just focus on the table below, you'll see that the technique here, the process was to make a single granulation, and then add the magnesium stearate after the granules are formed. So this is a single

granulation technique.

Q. All right. If we could quickly go back to PTX-844.7. And could you remind us again what this is?

A. So we used this a couple times. This is the formulation for the exhibit batch, EMM196. And as I've described a few times, this employs a double granulation technique, as you can see here, where magnesium stearate is the added in the first granulation and in the final lubrication step as well.

MR. LIEF: Before I go on, I would like to move the lab notebook we saw before this, PTX-288 into evidence.

MR. PETERKA: No objection.

THE COURT: Admitted without objection.

(PTX-288 was admitted into evidence.)

BY MR. LIEF:

Q. All right. I would like to turn to Plaintiffs' Demonstrative Exhibit 8.7. And can you tell me what is shown here?

A. So this is a demonstrative that I prepared to show the differences between the exhibit batch EMM196 and the formulation test batch F108. And what you see on the left is for EMM196 in blue and on the right, for the F108 tablet core formulations on the right column.

And what you basically see if you compare the

two tablets is that they have all the same ingredients in the same amounts, but if you, you know, look closely, you'll see, once again, that the EMM196 has a double granulation, and F108 has a single granulation and in EMM196, magnesium stearate is added twice, the first time in the inner or the first granulation step.

Q. Now, turning to the dissolution of these two, I would like to look at PDX-8.8. And can you describe what's shown here?

A. This is a demonstrative and a plot that I created to show the mesalamine release rate versus time of these two formulations. And keeping the same color coding, the squares and outlines in blue is the exhibit batch, and in green is F108, the test formulation.

And what you can see from these dissolution results is that F108 releases significantly faster, and that EMM196, of course, really is slower, and even at six hours, EMM196 is not releasing its complete payload of mesalamine.

Q. And what do you conclude from these results?

A. Well, by looking at the process and understanding that magnesium stearate is directly compacted into the inner granules of EMM196, I would conclude that the magnesium stearate in that inner volume is controlled at least compared to when it only put at the last lubrication

step.

Q. In terms of the source for this, I would like to look at DTX-303. And if we could look at DTX-303.7. And can you tell me what this is?

A. So when I constructed the plot, I looked at the original data, and this is the dissolution data for EMM196. And you can see it's for six tablets, and the three time points are in that left column. And that was the raw data that I used to prepare, part that I used to prepare the plot.

Q. All right.

MR. LIEF: Would have would move PTX-303 into evidence.

MR. PETERKA: No objection, Your Honor.

THE COURT: Admitted.

(PTX-303 Exhibit was admitted into evidence.)

BY MR. LIEF:

Q. And then I'd also like to turn to PTX-866. And I would ask you what this is.

A. So this is another Zydus laboratory notebook, notebook 3904, and this has the dissolution data that I use for the formulation and test batch F108.

Q. If we could look at page 866.164, going towards the bottom. Can you tell me what this is?

A. Yes. And so as you can see, this is for F108,

formulation test batch. Once again, for six tablets. And the six time points are in the left column, and this is the dissolution data over that six-hour time course.

MR. LIEF: All right. We would move PTX-866 into evidence.

MR. PETERKA: No objection, Your Honor.

THE COURT: It's admitted without objection.

(PTX-866 was admitted into evidence.)

BY MR. LIEF:

Q. Is there any other data from Zydus' ANDA that also supports your opinion that the magnesium stearate slows release?

A. Yes, there is.

Q. All right. If we could look at PTX-208, which was already in evidence, at page .24. What is shown here in this table?

A. So this is another test formulation, as you can see in this table. And I will just focus on the first two, the F044 and the F048.

And what you can see here is this is now where they studied the effect of compacting the mesalamine, which is that first row, with and without lubricants. And as you can see, there's an asterisk after the F048 lubricant amount and it says, contains nine milligrams of lubricants, and that's why it's 1209 milligrams instead of 1200.

Q. And how do you know the extra nine milligrams of lubricant is magnesium stearate?

A. Well, two ways. First, I looked at the ANDA, and the only way that Zydus refers to lubricants is with respect to magnesium stearate, but also I reviewed the laboratory notebook. That confirmed that as well.

Q. All right. If we could turn to the next page of this, 208.25, what is shown in the data and the graph there?

A. So what is shown here now is a dissolution of those four test batches, and it's going to require a little bit of explaining, but I think it must have been done in color originally, because you will see that there's two black triangles and two black squares.

But if you look in conjunction with the table above, you will see that the F044 has very fast release, and that is the black square that is to the far left, and that means -- that shows that the mesalamine was released more quickly than the other grouping of formulation that you see on the right.

And one of those, F048, and as you can see, F048 is a solid triangle down in the caption or legend, and you can see that falls to the right, and therefore it's showing slower dissolution of mesalamine.

And recalling that the magnesium stearate was

compacted into those granules, it's my opinion that this is what causes the slow release of mesalamine.

Q. All right. Turning to Dr. Hoag's testing, can you please explain for us what Dr. Hoag did?

A. Well, Dr. Hoag did a version of, you know, a standard fluid penetration or drop penetration test. And he looked at a simulated inner granule from that first compacted step.

He looked at, and I think we recall the process that he did to make these compacts. He took mesalamine and magnesium stearate and compressed them into a compact. He then compared the fluid penetration to the mesalamine compact by itself.

Q. And what --

A. Oh.

Q. Go ahead.

A. And what he observed was that the fluid up take into the simulated inner granule compact was about two-and-a-half times or so slower than mesalamine by itself.

Q. All right. And what conclusions do you draw from those results?

A. Well, once again, this is in support of magnesium stearate in that simulated inner granule or in the inner granule that Zydus would control the release of mesalamine by imparting lipophilic property to that material.

Q. Now, assuming that the distribution of magnesium stearate itself in the inner volume of Zydus' granule is deemed to be the matrix, does that distribution have lipophilic properties in your view?

A. Yes, it does.

Q. And for this question, I want you to assume differently.

Assuming that the inner matrix is deemed to be the magnesium stearate in there plus the other internal excipients, colloidal silicon dioxide, does that internal matrix have lipophilic properties?

A. Yes, it does.

Q. And what accounts for the lipophilicity of either of those regions in the Zydus granules?

A. The magnesium stearate.

Q. Okay. And does the colloidal silicon dioxide stop the inner matrix from having lipophilic properties?

A. No, it does not. The magnesium stearate is a potent lipophile, and it would overpower any effect, any of colloidal silicon dioxide, and therefore, in my opinion, it would not affect the lipophilic character and it's unrelated.

Q. If we could look at the patent, PTX-1. And I'd like to direct you to column 1 in the patent, around lines 42 to 47.

And can you tell us what this says, if anything, about silicon dioxide?

A. Well, this is a passage from the '720 patent, where they've already introduced the concept of the lipophilic matrix, and they show a couple examples. This is one of the first, where an ingredient, in this case, colloidal silicon dioxide, is used as a porization element, but they still refer to this lipophile as a lipophilic matrix.

THE COURT: Do you have an idea what a porization element is?

THE WITNESS: Sure. Absolutely.

So in this case you would have this lipophilic solid material, and the colloidal silicon dioxide would be dispersed in it and it would dissolve. And when it dissolves, it leaves a pore or a channel.

THE COURT: All right. Thank you.

THE WITNESS: You're welcome.

BY MR. LIEF:

Q. And given that statement in the patent and your view of the lipophilic properties of the inner region of Zydus' granules, in your opinion, is the colloidal silicon dioxide related or unrelated to the lipophilic property in there?

A. It's unrelated.

Q. And, Dr. Sinko, to change topics, does the magnesium

stearate and magnesium palmitate in Zydus' product melt below 90 degrees C in your opinion?

A. Yes. Based on what we just saw, the extensive analysis by Dr. Pinal, it's my opinion that magnesium stearate, magnesium palmitate, will melt below 90 degrees C.

Q. Now, for this set of questions, I want you to assume that the Court were to find that these substances don't literally melt below 90 degrees C.

Do you have an opinion as to whether they would be equivalent to a claim 1A substance that does melt below 90 degrees C?

A. Yes. It's my opinion that it would be equivalent, or they would be equivalent.

Q. What is your understanding of the doctrine of equivalents?

A. Well, counsel explained to me that this doctrine of equivalents applies when the difference between the claims and the infringing element are not substantial.

Q. And have you heard of something called the function, way, result test?

A. Yes, I have, and that has also been explained to me that an element would be considered an equivalent if it performs substantially the same function in substantially the same way to achieve substantially the same result.

Q. All right. I would like to look back at the patent

again, PTX-1, and I think the examples -- I think in column 4.

Are there any substances in these examples that are comparable to magnesium stearate or magnesium palmitate, in your opinion?

A. Yes. If you look at Examples 2 and 3, you'll see that there's stearic acid in Example 2, and palmitic acid in Example 3.

Q. Now, do those two substances melt below 90 degrees C?

A. Yes, they do.

Q. And are those substances -- well, let me do it in pieces.

Is stearic acid structurally similar to magnesium stearate?

A. Yes. There's a structural similarity.

Q. And is palmitic acid structurally similar to magnesium palmitate?

A. There's also structural similarity there, too.

Q. Okay. If we could look at PDX-8.9. Can you tell me what this demonstrative is?

A. So this is another demonstrative that I prepared to show the similarity between magnesium stearate and stearic acid. And what you can see is that stearic acid has an 18 carbon chain, and magnesium stearate would take two of those stearate anions and make the magnesium salt. And so they

are both lipophilic substances.

Q. All right. And if we could go to PDX-8.10. What is this?

A. Well, this is basically the same analysis with palmitic acid, a difference being palmitic acid has 16 carbons in that chain instead of 18.

Q. And if we could look at PDX-8.11, can you tell me what this demonstrative is?

A. So this was my analysis of the function, way, result for magnesium stearate, and it's my opinion that magnesium stearate controls release as an inner lipophilic matrix, and the way that it does this is by dispersion with mesalamine, you know, to cause this water repelling or water retarding effect, and it results in a controlled release profile, or dissolution profile, as described in the '720 patent.

Q. I would like to turn to the outer hydrophilic matrix. If we could turn to PDX-8.13.

All right. What is this?

A. So this is a demonstrative showing the construction of the claim 1B term, outer hydrophilic matrix. Once again, the agreed upon claim construction of matrix and hydrophilic.

For matrix, it was a macroscopically homogeneous structure in all its volume and hydrophilic has an affinity for water. And the Court has construed an outer

hydrophilic matrix to be a matrix that exhibits hydrophilic properties and is separate from the inner lipophilic matrix.

Q. And have you applied these constructions in forming your analysis?

A. Yes.

Q. And have you formed an opinion as to whether Zydus' product contains an outer hydrophilic matrix?

A. Yes. Zydus' product has an outer hydrophilic matrix.

Q. What in your opinion forms the outer hydrophilic matrix in the Zydus product?

A. Well, it's the distribution of the sodium starch glycolate and the carboxy methylcellulose sodium, these hydrophilic excipients in the region outside the inner granules.

Q. All right. If we could look at PDX-8.12. Take that out. I am going to stick with 8.13.

In 1B, does sodium carboxymethylcellulose fall into any of the categories of compounds listed in 1B?

A. Yes. It's a -- let me find it. It's a hydroxyakyl cellulose, carboxyalkylcellulose. Sorry.

Q. What about sodium starch glycolate? Does it fall within any of those categories?

A. Yes. It says starch. It's a starch derivative.

Q. All right. There's another chemical that goes into that.

A. Yes.
Q. Right. It's called hypromellose.
A. Yes. Hypromellose is hydroxypropyl methylcellulose, and that's used in the wet granulation, the binder used in the wet granulation, and that's a hydroxyakyl cellulose and could be considered a third hydrophilic ingredient in the outer matrix.
Q. All right. Do the ingredients in that outer region that result from the second granulation form a macroscopically homogeneous structure in all its volume?
A. Yes, they do.
Q. And what is the basis for your opinion in that regard?
A. Well, there is the, the Zydus process for manufacturing the product.
Q. If we could take a look at PTX-287.60. I believe this is the batch manufacturing record.
(Pause.)
MR. LIEF: 287.60.
BY MR. LIEF:
Q. And I would like to focus you in on the steps here and how, if at all, does any of this inform your opinion?
A. All right. So what you see here is, once again, the batch manufacturing record for the exhibit batch, EMM196. And you can see here that the, the compacted mesalamine from

that first compaction step is mixed with the hydrophilic excipients, carboxymethylcellulose sodium and sodium starch glycolate in 10.1, where they are actually mixing the ingredients together, which is dispersing that, those mesalamine granules within those hydrophilic excipients.

Q. All right. Have you formed an opinion as to whether Zydus' outer hydrophilic matrix -- once again, why don't I just call it an outer matrix for the time being. Have you formed an opinion as to whether Zydus' outer matrix exhibits hydrophilic properties?

A. Yes, I have.

Q. And what is that opinion?

A. And that it does exhibit hydrophilic properties.

Q. All right. If we could turn to PDX-8.14. What is shown here?

A. So in a similar way that I did for the definition of lipophilic properties, this is a demonstrative that I prepared that shows how the patent considers hydrophilic properties, and these are two portions of the patent.

One comes from the background of the invention, and the first passage states, the use of hydrophilic matrices in which the main component of the matrix structure opposes high resistance to the progress of the solvent, in that the presence of strongly hydrophilic groups in its chains, mainly branched, remarkably increases

viscosity inside the hydrated layer. And this is from the '720 patent, column 1, lines 21 to 26.

And, you know, what this shows is the, the -- in essence, the definition of hydrophilic in the patent. And it describes the mechanism by which it does it, which is the swelling.

And in this other passage of the patent, the detailed disclosure of the invention, it states, the hydrophilic matrix consists of excipients known as hydrogels, i.e., substances which pass from the dry state to the hydrated one, understanding the so-called 'molecular relaxation,' namely a remarkable increase in mass and weight following the coordination of a large number of water molecules by the polar groups present in the polymeric chains of the excipients themselves.

And this is the '720 patent, column 3, lines 18 to 24. And, once again, this shows what is considered a hydrophilic property, which is this, this swelling behavior.

Q. And does Zydus' outer matrix exhibit the properties described in these passages?

A. Yes, it does.

Q. All right. And what is the basis for your opinion in that regard?

A. Well, the basis for my opinion is that these are known hydrophilic substances that are -- they are known to

swell, and as, you know, Dr. Little had testified to, you know, he observed, you know, swelling in the tablet as well.

Q. All right. Have you formed an opinion as to whether Zydus' outer hydrophilic matrix is separate from the inner lipophilic matrix?

A. It's separate. Yes, I have, and it is separate.

Q. And what is your basis for that conclusion?

A. Well, I've looked through the manufacturing process and Zydus uses a double granulation technique, and what this shows is that, you know, two granulations, and so therefore two different areas or volumes that are not just compositionally separate, but spatially separate.

Q. And I'd like to turn to another element. If we could look at PDX-8.15.

THE COURT: I would just like to ask a question.

Would you repeat that, explain it? What is it about two granulation processes that, in your opinion, Dr. Sinko, resulted result in spatially different matrices?

THE WITNESS: Sure. So I showed an overview of the manufacturing process early on, and what you see in that first step is the formation of these compact granules with the mesalamine, colloidal silicon dioxide and magnesium stearate. The hydrophilic excipients are then added to that, and then a second granulation is made. And so you get

those inner granules are making new granules with the hydrophilic excipients surrounding them and kind of gluing them all in one place to make a larger particle.

THE COURT: All right. Thank you.

MR. LIEF: If it would help, we could go back to that demonstrative.

THE COURT: That's fine. I remember the demonstrative.

MR. LIEF: All right.

BY MR. LIEF:

Q. And so turning to PDX-8.15, now going to a new issue, what is this?

A. So this is the construction of the claim term dispersed as it's used in claim 1B of the '720 patent, and the Court's construction of this says sufficiently mixed to incorporate one substance into another.

Q. And have you applied this construction in performing your infringement analysis?

A. Yes, I have.

Q. And have you formed an opinion as to whether the inner lipophilic matrix is dispersed within the outer hydrophilic matrix of Zydus' product?

A. Yes. It's my opinion that the inner lipophilic matrix is dispersed in the outer hydrophilic matrix in Zydus' product.

Q. If we could turn back to the batch manufacturing record, 287.60, and focus in on Step 10.1.

Does this tell you anything about the relationship between the inner and the outer volume?

A. Yes, it does. This is one of the first steps where again you take the compacted mesalamine, which are the inner granules, and you're mixing them with the carboxy methylcellulose sodium and sodium starch glycolate in 10.1.1, and you're dispersing the inner in those outer hydrophilic excipients.

Q. I would like to turn now to another version of dispersed in the claim. If we look at PDX-8.16, what is shown here?

A. So this is showing the construction of wherein the active ingredient is dispersed both in the lipophilic matrix and in the hydrophilic matrix. And the Court construed that to be, wherein mesalamine is sufficiently mixed to incorporate it within the lipophilic matrix and the hydrophilic matrix.

Q. Have you applied this claim construction in your analysis?

A. Yes, I have.

Q. And have you formed an opinion as to whether this claim limitation is met by the Zydus product?

A. It is my opinion that the claim limitation is met by

this product.

Q. Again, going back to the batch manufacturing record, if we could look at 287.44.

What information is provided here in step 6.3?

MR. PETERKA: I'm going to object to this line of questioning. I think the satisfaction of the dispersed within the inner matrix is beyond the scope of Dr. Sinko's expert report.

THE COURT: Mr. Lief?

MR. LIEF: Give me a moment. I will look at his report. I have a note in my script about 136 and 140 paragraphs.

THE COURT: All right.

(Pause while counsel conferred.)

BY MR. LIEF:

Q. I will read to you from paragraph 134 of this report, which I think covers this, and I think this is -- I didn't think this was controversial anyway. But his report reads: "In Zydus' manufacturing process, the dense granules of blended mesalamine dash containing the magnesium stearate matrix dash are dry mixed with the outer hydrophilic matrix - the SSG and CMC- thereby dispersing the inner lipophilic matrix within the outer hydrophilic matrix.

Again, at the beginning of that, he's discussing the dense granules of blended mesalamine. The concept of

mesalamine as on the inside is inherent in that language.

THE COURT: All right. Please identify yourself for the record.

MR. PETERKA: I'm sorry. Do you want me to go back there?

THE COURT: That's fine. Come right up to the podium.

MR. PETERKA: Jim Peterka for Zydus.

There's no point in Dr. Sinko's report where he opines that the API is dispersed in the inner lipophilic matrix. And what he just read to you does not describe API dispersed in the lipophilic matrix.

THE COURT: API?

MR. PETERKA: I'm sorry. The mesalamine, Your Honor.

THE COURT: All right. Does it say mesalamine is dispersed? Why don't you give me the page number again. Do I have the report?

MR. LIEF: Do you have a copy of that?

(Pause.)

THE COURT: If I understood correctly, and while we're looking for that, he says -- why don't you give me that paragraph again, Mr. Lief.

MR. LIEF: The paragraph I read you was 134, and it reads, in Zydus' manufacturing process, the dense

granules of blended mesalamine. And certainly, blended here in our view and dispersed are --

THE COURT: Yes. So it says the dense granules of blended mesalamine are dispersed. And that is not sufficient to cover this testimony because of what, Mr. Peterka?

MR. PETERKA: The claim element is API, mesalamine is dispersed in both an inner lipophilic matrix and an outer hydrophilic matrix. The paragraph he is talking about here, he's talking what he's claiming is the inner lipophilic matrix.

THE COURT: Right.

MR. PETERKA: It's hard to tell what he's saying, but those are being dispersed within the outer hydrophilic matrix. All right? So that's talking about the claim term we looked at earlier, where it says, the inner lipophilic matrix is dispersed in the outer hydrophilic matrix. That paragraph does not go to whether mesalamine is actually dispersed in an inner lipophilic matrix.

MR. LIEF: Well --

THE COURT: This is actually dispersed with an outer hydrophilic matrix. Is that what you are saying?

MR. PETERKA: No. The paragraph 134 that Mr. Lief is just referring to, saying that -- I'm sorry, the dense granules are dry mixed with the outer hydrophilic matrix,

thereby dispersing the inner lipophilic matrix within the outer hydrophilic -- actually, I mean, I can show you this on Dr. Sinko's cross. If I can show you the claim term I'm talking about?

THE COURT: Yes.

MR. PETERKA: Can I see your demonstratives, please?

MR. LIEF: Your Honor, perhaps I can clarify some more.

MR. PETERKA: Well, can I just finish my explanation?

THE COURT: Yes. I'm going to let Mr. Peterka finish with his objection and I'm going to let you finish working out where it is in the report. All right, Mr. Lief?

MR. LIEF: Thank you.

MR. PETERKA: Could I have, I think it's PDX-8.15.

That's what he's talking about there. He's talking about in that paragraph 134. I think that what is trying to talk about, that claim term. I'm not saying that is what he's saying, I'm saying that is what he's referring to.

What I'm referring to is the claim term we were just looking at, at the end here. It's actually in part 1A,

at the end of the claim. Wherein the active ingredient is dispersed both in the lipophilic matrix and in the hydrophilic matrix.

What I'm saying is the opinion that active ingredient is dispersed in an inner lipophilic matrix is outside the scope.

THE COURT: All right. Mr. Lief?

MR. LIEF: Well, two responses. I think what I read is responsive because it talks about blended mesalamine. But apart from that --

THE COURT: No, no. Say that again. Don't go apart from that. Give it to me again.

MR. LIEF: Well, what I read, although I have a more poignant thing to read to you, but what I read from what's paragraph 134 from his 2014 report.

THE COURT: Yes. And am I going to get to see that?

MR. LIEF: Oh, I apologize. But what I also want to give you is the 2012 report, but if I may?

THE COURT: All right. I would like to see what you were reading from so I can see it in context.

(Mr. Lief handed documents to the Court.)

THE COURT: And while they're getting that, what is it you want to point me to in his 2012 report?

MR. LIEF: Where I was reading from was

paragraph 134, which is on page 52, which reads -- I think it covers both of these dispersed issues, candidly, but in Zydus' manufacturing process, the dense granules of blended mesalamine. That's the inner product of that first compaction step.

And so when it says blended mesalamine, you can stop there. The rest of it relates to dispersed, inner dispersed and outer. But blended mesalamine and the dense granules means --

MR. PETERKA: Your Honor, I'm going to object. This is attorney argument characterizing Dr. Sinko's opinions.

THE COURT: Well, of course it's attorney argument. I've asked for attorney argument.

MR. PETERKA: All right.

THE COURT: You don't have to object.

MR. PETERKA: All right.

THE COURT: Let him finish. I will give you a shot.

MR. LIEF: And so I think dense granules of blended mesalamine is what we're talking about, but if you want the exact word "dispersed," you know, this is a long case, it has been going on for a while, and Dr. Sinko submitted an earlier expert report on what was the earlier batch, which as their 30(b)(6) said, all of that information

applies equally to the new batch.

And I have that 2012 report now. If I might approach and hand you that?

THE COURT: Sure.

(Mr. Lief handed documents to the Court.)

THE COURT: What do you want me to look at in this one?

MR. LIEF: And in the 2012 report, we have a paragraph 107, which comes under a heading, and this is on page 46. The heading is, "The Zydus ANDA product contains active ingredient dispersed both in the lipophilic matrix and the hydrophilic matrix."

And paragraph --

THE COURT: I'm looking at 107. I got the --

MR. LIEF: On page 46 of the new one I just handed, the 2012 report.

THE COURT: Yes. Where were you reading?

MR. LIEF: I was reading letter G above 107 is the title.

THE COURT: Okay.

MR. LIEF: And then 107 says, quote, "The Zydus ANDA product contains active ingredient dispersed (distributed more or less evenly) in a lipophilic matrix.

And it goes on to describe. It says, "Described above, magnesium stearate and colloidal silicon dioxide are

first blended with mesalamine in an eggshell blender."

This is the exact thing he's testifying about. I mean, candidly, this is one of the bits of infringement proof, and Dr. Sinko, I don't think we would have missed this in his reports.

THE COURT: Yes. All right.

Mr. Peterka, your last shot. Go ahead.

MR. PETERKA: Your Honor, in the expert reports from 2012, which was paragraph 107 there, you'll see that Dr. Sinko does have those words, "Zydus' ANDA product contains active ingredient dispersed (distributed more or less equally in a lipophilic matrix).

Number one, that same term has subsequently been construed to mean sufficiently mixed to incorporate one substance into another. That was actually an earlier proposed claim construction by the plaintiffs in this case, and that Your Honor did not grant them, that construction.

And also that opinion does not appear in his more recent supplemental infringement report on the current batch in any sense of the claim construction.

THE COURT: Yes. Okay. Well, I'm overruling your objection. You can make whatever hay you can make out of it on cross-examination, but I think you guys are on notice. And I agree with the assertion that the 2012 report

is not off the table, it's part of the mix here, and what you should be thinking about in terms of the reports that you received.

MR. PETERKA: If I could just make one more point.

Dr. Sinko in his reports has no opinion on whether that term has been satisfied under the Court's claim construction.

THE COURT: I will let you make -- I will let you make your argument, but I'm not going to keep him from testifying. All right? You can go ahead and make that pitch to me, but I'm not ruling his opinion out of order and keeping it out of the record.

MR. PETERKA: Thank you, Your Honor.

THE COURT: All right. Why don't we hand these back to Mr. Lief. And you go ahead and proceed.

MR. LIEF: Thank you, Your Honor.

BY MR. LIEF:

Q. I think we were in PTX-287.44, and we were looking at Step 6.3.

And what information does Step 6.3 provide you with respect to mesalamine dispersed in the inner matrix?

A. Well, this is from a batch manufacturer record. It shows that first granulation step, the dry granulation and

roll compaction step.

What you are going to see where and what I described before is the that mesalamine, which is part of that mixture from the prior step, is compacted into the inner granule. And then if you look at 5.3.4, there they're then milled or sized, and you can see the size of the screen, 8.4 millimeters, and that's going to produce, or allow granules of that size or smaller through as well as fines.

Q. All right. Before we get to the granules and the fines, the mixing steps that lead up to 6.3 and then the granulation or the compacting, I should say, in the 6.3, if we could go back to PDX-8.16.

Will that incorporate mesalamine within the lipophilic matrix?

A. Yes, it does. It's in the -- it's in the first granules, which, as I said, contains the lipophilic matrix.

Q. All right. And to go back to the batch manufacturing record, I would like to change pages and go to 287.60.

Now, this is, I think this is step 10.1. Does this inform your opinion in any way about mesalamine in the outer matrix?

A. Yes, it does. So this, this in essence starts now with, as you can see, the compacted mesalamine, which

includes those inner granules, but also includes the fines, and the fine particles of mesalamine. And that mixture is mixed or dispersed with the carboxymethylcellulose sodium and sodium starch glycolate and made into the second granulation, and so therefore it disperses mesalamine in the outer matrix as well.

Q. All right. Talk about fines. I would like to go to PTX-292. And can you tell me what this document is?

A. This is the manual for the roll compactor machine used by Zydus in producing their ANDA product.

Q. All right. And if we look at 292, page .07, there's the last sentence there that I would like you to read for us and tell us what you take from it.

A. The last sentence says, "The addition of binders to the material being processed greatly reduces the production of fines." And what this, you know, basically reenforces is that, you know, these granulation techniques, because of the filter -- I mean, sorry, the sieve that's used, it allows fine particles to be passed through there and be produced.

And what this is saying is that in this general manual, you could use binders to reduce the amount of fine, but Zydus does not use a binder in that first compaction step and so it will have a characteristic normal amount of fines.

MR. LIEF: All right. If we could move PTX-292 into evidence.

MR. PETERKA: No objection, your Honor.

THE COURT: All right. It is admitted without objection.

(PTX-292 was admitted into evidence.)

BY MR. LIEF:

Q. Now, again, on this issue of mesalamine being on the inner compacted region and in the outer region, are you aware of any other evidence that supports your opinion in this regard?

A. Yes. I've also seen some testing results by Dr. Davies.

Q. And what do you conclude from Dr. Davies' testing results?

A. Well, Dr. Davies did a Raman analysis and he showed that the mesalamine was, you know, dispersed throughout the tablet.

Q. All right. If we could go to PDX-8.17.

Dr. Sinko, does the Zydus ANDA product, in your opinion, literally infringe claim 1 of the '720 patent?

A. Yes, it does.

Q. And turning to claim 3, compositions as claimed in claim 1 in the form of powder, capsules, mini tablets, does the Zydus ANDA product literally infringe claim 3 of the

'720 patent in your opinion?

A. Yes, it does.

Q. And, again, if we were to assume that the melting point of magnesium stearate in the Zydus product were to be found to be literally not below 90 degrees C, in your opinion, would the magnesium stearate be an infringing equivalent?

A. Yes, it would.

MR. LIEF: Okay. Thank you. No further questions.

THE COURT: Mr. Peterka, cross-examination.

MR. PETERKA: Give me one second, Your Honor.

THE COURT: Sure.

(Pause while counsel conferred.)

MR. MILLER: May I approach?

THE COURT: Yes, you may approach.

While we're waiting, I'm going to ask a question, too. I will ask the last demonstrative be put up on the board.

MR. LIEF: The checkmarks?

THE COURT: The checkmarks.

You probably said something about this Dr. Sinko, but I'm curious to know about the 80 to 95 percent related total composition. What were you relying on then?

THE WITNESS: This was the Zydus ANDA, and if I recall, it was 81.91 percent mesalamine.

THE COURT: Mesalamine. All right. Thanks.

MR. MILLER: Approach the witness?

THE COURT: Yes, please.

(Mr. Miller handed a notebook to the witness.)

MR. PETERKA: Good afternoon, Your Honor.

CROSS-EXAMINATION

BY MR. PETERKA:

Q. Good afternoon, Dr. Sinko.

A. Good afternoon.

Q. Good to see you again. For the record, Jim Peterka for Zydus again.

Dr. Sinko, you were retained by Shire as an expert witness in other cases related to generic versions of Lialda; is that correct?

A. That is correct.

Q. And that includes a case against Watson?

A. That is correct.

Q. And, in fact, you just testified on behalf of Shire in a recently concluded trial that took place in January; is that right?

A. That is correct.

Q. And you were present at the Shire trial and the testimony Dr. Yang?

A. Dr. Yang, yes.
Q. Dr. Yang. Dr. Yang was another expert witness on behalf of Shire; is that correct?
A. He was.
Q. And in that trial, you relied on Dr. Yung's tests, or Yang's, I'm sorry, in forming your opinions in that case?
A. Yes, I did.
Q. And part of your opinions in that case included an opinion that the granules in the Watson product exhibited lipophilic characteristics; is that correct?
A. That's correct.
Q. The tests that were conducted by Dr. Yang, that was a drop penetration test, is that right, or a water penetration test?
A. Yes. Fluid penetration test.
Q. And Dr. Yang conducted those tests to examine that the ANDA, that the Watson ANDA product contains separate volumes separated in a different capacity to resist water penetration; right?
A. That is correct.
Q. In the Watson case, Dr. Yang tested an actual cross-section of the Watson ANDA product; is that correct?
A. He applied, yes, his specific test to a cross-section of that product.

Q. So the test that Dr. Yang used in that case that you relied on involved taking an actual tablet of the Watson product, cutting it in half, cutting it in two halves, microtoming it to get a smooth surface, using a microscope to identify certain structures in that cross-section to be tested, and then placing the drop of water on the selected structure and measuring the water penetration rate; is that right?

A. Well, kind of. I mean, what he did was, he used a much smaller version of the test, so it was, instead of like a catheter tube, which is bigger, microgoniometer. You could precisely place very small drops, and that's why he could do it on the Watson ANDA product.

Q. The microgoniometer, that's the device that's used in the Hapgood reference that you cited in your most recent expert report; is that correct?

A. I don't recall that she used a microgoniometer.

Q. She used an actual, a drop of water; is that right?

A. Well, all of these tests look at some sort of water or fluid, and the size of the drop, you know, could be different. And as I recall, Dr. Hapgood and I didn't review that recently, but I think Dr. Hapgood did a regular drop penetration test and Dr. Yang used a microgoniometer so he could precisely place a microdroplet on that product.

Q. And the structures that Dr. Yang identified in the Watson case were granules; right?

MR. LIEF: Your Honor, I guess I object. This is already now getting into details of what really is another case.

THE COURT: Well, I think it's going -- I think it is fair cross-examination, Mr. Lief, so I'm going to allow it.

Go ahead.

MR. PETERKA: Thank you, Your Honor.

BY MR. PETERKA:

Q. Do you remember the question? I can repeat it.

A. Yes. Why don't you repeat it.

Q. The structures that Dr. Yang identified in the Watson case were granules; is that correct?

A. Yes. So first let me say, I've not gone back and reviewed the whole Watson case, so my memory may not be really fresh, but he identified two regions. He defined granular regions and extragranular regions, so not just granular regions. He identified two different types of regions.

Q. And Dr. Yang also identified cross areas in Watson's tablet that were outside the granules; is that correct?

A. That's what I just said.

Q. All right.

A. So he identified what he called Type 1 regions and Type 2 regions, which I could identify as granular and extra granular.

Q. And you testified in that case that the test results showed that the granule structures that he identified took up water almost seven times more slowly than the structures that were outside the granules; is that correct?

A. Well, like I said, I don't recall seven, but the granules definitely took up fluid more slowly.

Q. And the water -- let me skip that.

Now, in this case, none of Shire's experts, including yourself, have performed any drop penetration testing on a cross-section of Zydus' ANDA product; is that correct?

A. Dr. Hoag did a version of the drop penetration or fluid penetration test in the simulated, you know, inner granule.

Q. All right. So the answer to that question is no; is that right?

A. No expert on Shire's side that I know took the actual ANDA product and performed a similar test. I think they -- you know, Dr. Hoag performed a similar informative test.

Q. So no expert in this case performed a test on a cross-section of the Zydus product; is that correct?

A. No.
Q. Okay. And no expert in this case performed any drop penetration testing on the Zydus ANDA product at all; is that right?
A. Well, I think as I said, they, Dr. Hoag performed a test on the simulated granule, but not on the actual ANDA product.
Q. In that same case that we were just talking about, the Shire versus Watson case, Dr. Bugay was another expert retained by Shire; is that correct?
A. That was a long time ago. That was the first trial.
Q. Yes. That was in 2013; right?
A. 2013.
Q. So do you recall him being an expert in that case?
A. Absolutely.
Q. And he also did testing on the Watson ANDA product that you relied on in forming your opinions; is that correct?
A. Yes.
Q. And the opinions in that case included the opinion that Watson's product contained an inner lipophilic matrix and an outer hydrophilic matrix; is that correct?
A. You know, back in -- I've not reviewed that, and I don't recall the specific details, but I do recall Dr. Bugay being there and some chemical analysis and things.

Q. What about more recently? Didn't that come up in a more recent trial, too, in January? You opined that Watson's product contained an inner lipophilic matrix and an outer hydrophilic matrix?

A. Yes, I did.

Q. I think Dr. Bugay's testing came up there as well.

A. It may have come up in the context of the previous trial.

Q. If you can turn in your binder, I think there are trial transcripts in that binder.

Do you see, I think they're identified by Day 1, Day 2, Day 3. I think Day 1 was January 25th, 2016.

THE COURT: Is it all under the tab, Sinko transcript?

MR. PETERKA: No, there should be a trial transcript. Oh, yes. You're right. It's in the binder under Sinko. Do you mind if I take a look? Actually, I've got one right here.

THE WITNESS: Yes, there are two tabs.

MR. PETERKA: Oh, no. It's under --

THE COURT: Do you want a copy of this?

MR. PETERKA: I have a copy. Apparently, I didn't get a paper copy in the binder, but I have it on the screen. It is going to be a pretty easy point, if Your Honor will indulge me for not including it in the binder.

THE COURT: Well, I'll indulge you. I'll wait and see if they indulge you.

MR. LIEF: That's fine, assuming that we get the same courtesy on cross if we miss something in our binder.

THE COURT: Yes, sure. Go ahead.

BY MR. PETERKA:

Q. If you could go to, it's page 222. And then toward the bottom there.

So this is your testimony in that trial. If you go, actually go to the first page, page 3 of the transcript.

Do you see direct examination of Dr. Sinko by Jason Lief? Starting on page 193.

A. Yes, I do.

Q. So now if we can turn -- that is 193 to the end of the transcript, I'll just represent. If you can go to page 222. At the bottom paragraph there, lines 17 through 21.

Do see there, you reference Dr. Bugay's SEM and SEM-EDX pictures?

A. Yes, I do.

Q. Does that refresh your recollection that you relied on Dr. Bugay's testing?

A. Yes, it does.

Q. Now, the testing that Dr. Bugay did, he used, as it says there, SEM and EDX to locate and map the excipients in the cross section of the Watson ANDA product; correct?

A. Yes, he did.
Q. Specifically, he mapped the location of magnesium stearate and sodium starch glycolate in a cross section of the Watson ANDA using SEM and EDX; correct?
A. Yes, I believe so. I mean you just showed me one part of it. But, yes, I think so.
Q. Okay.
THE COURT: So maybe, I might have heard this acronym before, but, Dr. Sinko, do you want to tell me what SEM and SEM-EDX stand for?
A. Yes. So SEM is Scanning Electron Microscopy. And it's a technique that was used to look at the topography of the tablet.
And the SEM-EDX is where they, I think it's electrode dispersive x-ray, something like that. And this is where you can now, using the same machine, map the chemical signal with that topography that you take a picture of with just the SEM. So it maps a chemical map on top of a map of the tablet.
THE COURT: Okay. Thank you.
Thanks for indulging us, Mr. Peterka.
MR. PETERKA: Thank you, Your Honor.
BY MR. PETERKA:
Q. Dr. Burgay's SEM-EDX testing, which is a test you were just showed, as you said, he was able to identify where

in the cross-section of the tablet magnesium stearate was; right?

A. That's correct.

Q. And he was able to identify where in the cross-section sodium starch glycolate was as well; right?

A. Yes, they have different chemical signals.

MR. PETERKA: For the court reporter, sorry, sodium starch glycolate.

THE COURT REPORTER: I got it. Thank you.

MR. PETERKA: So SSG if we use it again.

BY MR. PETERKA:

Q. Now, in your opinion, Dr. Bugay's SEM-EDX in that case showed that magnesium stearate was homogeneously distributed throughout the volume of the granule that you contended contained the inner lipophilic matrix; correct?

A. That is correct.

Q. And magnesium stearate was the excipient that you contended formed the inner matrix in Watson; right?

A. Well, it was -- magnesium stearate was, once again, the potent lipophile that was distributed that would cause that behavior, that lipophilic character in that matrix.

Q. It was one of the things you were looking for the lipophilic matrix; right?

A. Yes, it was.

Q. So you were actually able to see it in the

cross-section of the tablet in that case; right?

A. Well, there is two things. I mean, first, there was the Watson process, and that was suggestive of where it was located but, in addition, there was the visual evidence as well as the testing that Dr. Bugay did.

Q. And magnesium stearate is actually the same material that -- it's a little unclear from your testimony earlier, but it appears you are contending that is the lipophilic matrix in Zydus's product; right?

A. Are you asking me if magnesium stearate is the lipophilic matrix in Zydus's product or are you going back to Dr. Bugay?

Q. Here in this case.

A. Oh, yes.

Q. So magnesium stearate is the same substance you were saying is either in the lipophilic matrix or is part of the lipophilic matrix, in both cases; right?

A. In both situations in this case, yes.

Q. What do you mean? I'm talking about --

A. Are you talking about --

Q. So Watson, you said the magnesium stearate --

A. Oh, that kind of cases.

Q. Yes. Oh, I'm sorry.

A. Yes. Do you want to repeat the question?

Q. Yes. So in the Watson case, there is the same

material, magnesium stearate that you were saying either was or was part of the lipophilic matrix there; right?

A. I believe that in the Watson case, they used some sort of commercial grade of magnesium stearate. I don't know if it's the same manufacturer or whatever as in the Zydus product, but it was magnesium stearate, meaning the mixture.

Q. And the Zydus product also contains sodium starch glycolate; right?

A. The Zydus product does, that's correct.

Q. Did you know that Dr. Bugay was identified as an expert in this case by Shire but never submitted a report?

A. In the Zydus case?

Q. Yes.

A. No, I did not.

Q. Now, Dr. Davies did some testing in this case; right?

A. Yes, he did. As I testified just a few minutes ago, he looked at mesalamine dispersion.

Q. He only looked for mesalamine; right?

A. That's all I'm aware of.

Q. So none of Shire's experts submitted any testing in this case in which they mapped the location of any non-active ingredient excipients of Zydus's ANDA product; correct?

A. I'm not aware that they did. But like I said

earlier, based on the process, I'm not sure if it was necessary.

Q. And that would include magnesium stearate?

A. In terms of --

Q. Mapping?

A. -- chemical mapping or ...

Q. (Nodding yes.)

A. That would include magnesium stearate.

Q. That would also include sodium CMC; right? Sorry. Sodium CMC.

A. It would be the same answer. It would include sodium CMC.

Q. You have never performed roller compaction, have you?

A. I have not personally performed roller compaction, but this is something that I taught over the years in the various courses as just one of the techniques of compaction. I mean of granulation. I'm sorry.

Q. You never even have been in the same room as a roller compactor; right?

A. Well, I may have been. I mean I don't recall.

Q. If you could turn to your binder there. I think we do have these transcripts. It's your 2014 transcript. Page 36.

A. Which tab?

Q. It says Sinko 2014. Sinko transcript 2014. If you

go to lines 8 through 16.

You recall being deposed in this case; right?

THE COURT: What page are we on?

MR. PETERKA: We are on page 36.

BY THE WITNESS:

A. 36.

Q. Yes. Do you recall being deposed in this case, Dr. Sinko?

A. Yes, I do.

Q. And I was there. I asked you questions and you gave answers; is that right?

A. Yes, that's correct.

Q. And you were under oath?

A. Yes, I was under oath.

Q. And do you see that, where it says:

"Question: You never witnessed -- aside from videos, you have never personally seen or witnessed a roller compactor being run, right?

"Answer: I've not been in the same room as a roller compactor."

A. Yes. As I just said, you know, I could have been in a room but, yeah, that is probably a fair assessment.

Q. And you have never analyzed the material produced by a roller compactor, have you?

A. From what perspective?

Q. Well, you have never personally looked at the material or felt it or investigated its components or its characteristics, have you?

A. Well, I mean at some level, that is not true. I mean I've, you know, I've looked at papers and have studied those papers and understand the processes. I mean, otherwise, how can I convey these things to different student groups that I have talked about granulation techniques to? I don't recall all the specific details, but I have reviewed papers.

Q. I'd like to talk to you about the matrix you testified about earlier. Right? And I'll be honest, I'm a little unclear from your direct examination. What is it in the Zydus ANDA product that you contend is the inner lipophilic matrix?

A. It's the distribution of magnesium stearate in those inner compacted granules.

Q. So now, in your opinion, those granules, the compacted granules you just referenced, those are also a macroscopically homogeneous structure in all their volume; correct?

A. I'm sorry. Could you repeat that?

Q. The granules you just referenced, right?, those granules are a macroscopically homogeneous structure in all their volume?

A. Well, as I stated before, because of the mixing steps

and the compaction of locking them in, the magnesium stearate would be homogeneously distributed within that volume.

Q. Right. And I'm asking the granules themselves would be, in your opinion, they would be a macroscopically homogeneous structure in all their volume; right?

A. Well, it's the volume in the granule.

Q. I'm asking you, so you understand the Court has construed the claim term "matrix" to mean "macroscopically homogeneous structure in all of its volume?"

A. That's correct.

Q. So where is the macroscopically homogeneous structure in all of its volume?

A. Well, that is the distribution of magnesium stearate in that volume which is in the granule.

Q. Okay. And the granule itself, in your opinion, would also be a macroscopically homogeneous structure in all of its volume; right?

A. Well, it would contain that distribution of magnesium stearate.

Q. Is the granule a structure?

A. You mean just in general?

Q. Yes.

A. Well, just in general, of course it is a structure.

Q. And in your view, is that granule macroscopically

homogeneous in all of its structure?

A. Homogeneous with respect to?

Q. I'm just asking, can you say yes or no to that?

A. Well, if you are going to talk about magnesium stearate, the magnesium stearate is homogeneously distributed at a volume because it's well mixed. And then by compacting it, it's locking it in that homogeneous distribution in that volume. That volume is in the granule.

THE COURT: I'm going to ask the question, too, because it is important to me.

THE WITNESS: Sure.

THE COURT: Is the granule itself macroscopically and homogeneously distributed throughout the pharmaceutical compound? And I don't have the exact words in front of me but I understand Mr. Peterka to be asking not about magnesium stearate separately but about the granules which they compact in.

If I have understood your question right.

THE WITNESS: Oh.

THE COURT: But even if I haven't understood it, that is what I'm interested in knowing. Are those granules -- do you want to give me the wording of that?

Thanks.

Are the granules "a macroscopically homogeneous structure in all its volume?"

If that is not a question that can be answered yes or no, that's fine. I'm not suggesting you have to answer it yes or no, but I would like to know whether you can answer that question are the granules, themselves, "a macroscopically homogeneous structure in all its volume?"

Now, I apologize because that is the definition of "matrix" I'm working with, and that is what I'm trying to figure out. Are those granules macroscopically homogeneous throughout?

Do you understand what I'm trying to get at? It is perfectly fine to say you murdered that question. I have no idea what you are saying.

THE WITNESS: Yes, it is not entirely clear to me. You mean like within, are the granules distributed through the volume of the tablet?

THE COURT: Yes. The matrix is defined, has been defined. The matrix itself is a macroscopically homogeneous structure in all its volume. Now I'm trying to figure out, are the granules themselves distributed within that matrix homogeneously throughout?

If you can answer that question, great. If you can't, that's okay, too.

THE WITNESS: So are the granules distributed through that matrix?

THE COURT: That's my question, or are the

granules somehow themselves the matrix? What are the granules in all this?

I hear you two sparring over magnesium stearate, but I'm interested in the granules that are in there. Are they, themselves, do you contend them to be the matrix? Do you contend them to be part of the matrix? Are they homogeneously distributed throughout the composition itself so they can be considered a matrix? I'm kind of curious about that, given the back and forth.

THE WITNESS: Well, I think that my point of reference has been for the inner matrix. We're talking about the inner lipophilic matrix is within the granule. And so I guess it would be closer to the granule than to the whole tablet, if I'm understanding correctly.

THE COURT: I apologize. I hijacked your examination for a moment, Mr. Peterka.

MR. PETERKA: No, any time.

BY MR. PETERKA:

Q. So as I'm hearing it, and again I'm a little confused, even after all these years, it's your opinion that the inner lipophilic matrix in the Zydus ANDA product is the dispersion of a single excipient in the volume of the granules; correct?

A. Of the magnesium stearate, that's correct.

Q. Correct. Okay. Now, in the distribution of

magnesium stearate that you contend is the matrix, the particles of the magnesium stearate are not interconnected; correct?

A. Are you asking if the magnesium stearate was somehow covalently bound and makes it a continuous structure?

Q. If you want to use the word covalently bound, that's fine. I'm asking if they're connected in any way.

A. Well, they're distributed throughout the volume but they're not physically interconnected.

Q. Actually, can I see DDX, the one with the flowchart. DDX -- I'm sorry. PDX-8.3.

Can I get a blow up of that picture on the upper right, the lipophilic granules and fines?

Actually, back up. I'm sorry. Back out.

BY MR. PETERKA:

Q. So as I understand it, your mesalamine is brown, tan. And the colloidal silicon dioxide is blue, and magnesium stearate is green', right?

A. Yes. I can't see that from here, but ...

(Chart blown up of color legend.)

Q. Okay. Am I right?

A. Yes.

MR. PETERKA: Okay. Can I get a blow up of the granules then?

BY MR. PETERKA:

Q. So each of those is, am I correct in determining those are all, each of the bigger circles there, those are granules?

A. Yes. So the bigger circles are the roll compacted granules containing those ingredients.

Q. Containing the mesalamine and the magnesium stearate and the colloidal silicon dioxide; right?

A. That's correct.

Q. And the magnesium stearate are the green dots in there?

A. Yes.

Q. So it's those three green dots in the granule that are the inner lipophilic matrix in the Zydus ANDA product in your opinion; correct?

A. Well, I didn't make this demonstrative to say that there is three magnesium ions in there. This was just to show that the magnesium was incorporated in there.

As you know, this is not a physical connection. We're now talking about in essence a chemical potency, and so each of these can be distributed throughout the volume, and they repel water because they have this region around them by which they can repel that water. It is not a physical connection.

I'm not saying that there is three in each one.

Q. So those three green dots in that image, taking one

granule, for instance. If I had a laser pointer -- I don't have a laser pointer, but take the one on the far right, about a third of the way up on the far right, it kind of sticks out. Do you see it?

A. Yes, I do.

Q. Okay. Those three green dots in that granule, those three green dots in your opinion are a macroscopically homogeneous structure in all its volume?

A. Well, first, we're looking at -- No. 1, I'm not representing that there is only three. No. 2, this is, of course, now a two-dimensional drawing. This was not -- this was meant to be a conceptual slide. I did not make -- I did not calculate, for example, how much magnesium stearate would be in, and then make a simulated granule, and then make a three-dimensional construction of it. This was just a concept to show that it was inside the granule.

Q. So if this is a representation of the granules, is that a yes or no to my question? Those three dots, that is the macroscopically homogeneous structure in your view; right?

A. As I said, it's not three dots. But those three dots are represented here conceptually, but it is not obviously three dots or three in series.

THE COURT: And I'm hijacking again.

And the word is "in all its volume." What is

the "its?"

THE WITNESS: Well, in this case, it would be within the volume of the granule.

THE COURT: That granule. That is the "its" there; right? And I understand all you said about it being conceptual, et cetera, et cetera; but if we were to take that granule, that would be, what you saying is that the magnesium stearate is homogeneously distributed throughout the volume of that granule?

THE WITNESS: That is correct.

THE COURT: Okay. I don't know whether that helps you at all, but it helps me. Thanks. Go ahead.

BY MR. PETERKA:

Q. So, in your opinion, the "its" in the construction "macroscopically homogeneous structure in all its volume" is the granule?

A. Well, I think the point of reference here is, we're talking about right here, the point of reference is the granule.

Q. And that is what I'm asking. So the "its" in the "macroscopically" --

A. Then please clarify because I'm not following.

Q. Judge Jordan just asked what is the "its?" And I'm just following up on it. The macroscopically homogeneous -- forgive me if I mispronounced that. The "homogeneous

structure in all its volume." The "its" in that phrase is the granule in your opinion; correct?

A. Well, no. When you ask at that level, we take the structure within "its" volume, "its" volume. It's -- maybe I'm not seeing it the same way. To me, it is the distribution of the magnesium stearate which creates a volume and that volume is in the granule, so that is what you are saying, and that is correct.

Q. Well, I'm not sure that was an answer but ... Do you understand how that term has been construed here?

A. "Its?"

Q. "Matrix." Do you understand how the term "matrix" has been construed here?

A. Yes.

Q. "Matrix" means a macroscopically homogeneous structure in all its volume." Correct?

A. That is correct.

Q. All right. And the "its," as I'm hearing from you, the "its" in your opinion, all its volume is the granule, right?, in the Zydus product?

A. A homogeneous structure and all its fines. So the structure is homogeneous in its volume, and that volume is inside the granule.

Q. What is the "its?" Can you tell me what the "its" is or no?

A. The matrix, the distribution of the magnesium stearate. I mean with respect to what we were just talking about.

Q. So in your view, the "macroscopically homogeneous structure in all its volume" is the dispersed particles of magnesium stearate on their own; right?

A. Yes, that is what I call three-dimensional dispersion. That creates a volume. That volume is in a granule.

Q. Okay. And where is the structure?

A. The three-dimensional structure or distribution.

Q. So in your view, the distribution of the magnesium stearate in the granule is "a macroscopically homogeneous structure in all its volume?"

A. That's correct.

Q. Now, the magnesium stearate particles that make up the inner lipophilic matrix, those are held in place by the mesalamine granule; correct?

A. Well, I mean the granule is a physical structure and it contains mesalamine and colloidal silicon dioxide and magnesium stearate.

Q. So is that a yes?

A. Are you saying does it physically?

Q. Does the magnesium stearate particle -- the magnesium stearate particle we were just looking at the illustration

of, those are held, the particles are held in place by mesalamine; right?

A. Well, I would say that all three excipients are compacted together. So does it, is there a special bond between the mesalamine and magnesium stearate? No. But they're compacted. They're there. They're collocated, so mesalamine is in place with the magnesium stearate and vice-versa.

Q. If you can go to the same deposition you were just at, page 167.

A. 167.

Q. Yes. Lines 5 through 12.

"Question: So is it your testimony that the particles of magnesium stearate are held in place by mesalamine that is in the granule? Correct?

You said:

"Answer: They have to be because mesalamine makes up most of the granule. That just happens to coincide with the volume of the inner lipophilic matrix.

A. What lines?

Q. Five through 12.

A. Well, that's what I was saying now. Yes, actually it's up there right there.

So there is no dispute for me that, I mean the product is 80 to 95 percent mesalamine, and there is

mesalamine in the Zydus product, there. Is mesalamine and there is magnesium stearate, and there is colloidal silicon dioxide.

So I don't see the issue. I mean clearly when they're compacted together, that is the entire point of granulation is to bring together different particles of ingredients and make a larger particle, and that is what this is. This is granules of larger particle of these three ingredients in the Zydus product.

Q. If you take away the mesalamine, you would no longer have a three-dimensional volume of magnesium stearate; correct?

A. You wouldn't have granulated, you just have the ingredient, one of the ingredients that you started with.

Q. And if those ingredients, the magnesium stearate, took away the mesalamine, the magnesium stearate would not be in a three-dimensional volume; is that right?

A. Well, if you only have magnesium stearate in a pile, it would still be a three-dimensional volume, high level magnesium stearate.

Q. Okay. And a pile of magnesium stearate is not a matrix; right?

A. Well, I mean, I guess if you look at the patent, I guess it would be a homogeneous structure in that volume of the pile.

Q. The three ingredients in the granules that form the compaction step in Zydus' ANDA product, mesalamine, magnesium stearate and colloidal silicon dioxide, they're all homogeneously distributed in granules in your opinion; is that correct?

A. The three ingredients, yes.

Q. May I have DTX-18? I think it's in your binder.

A. The binder you gave me?

Q. Yes. I think it's labeled in DTX-18 in the binder.

A. Okay.

Q. I think you looked at this page earlier, but I want to go to page, internal page 235660, the three ingredients there for the compaction step.

Can you actually highlight the whole row?

A. 660?

Q. Yes. Yes, 660.

A. Sure.

Q. You see there, are those the three ingredients in the compaction step? Colloidal silicon dioxide is in higher quantities than magnesium stearate is in the compaction step; is that correct?

A. Yes. It's per tablet. It is five versus four milligrams.

Q. So yes?

A. Yes.

Q. Now, back to the granule we were talking about. All of those, those three ingredients, the mesalamine, colloidal silicon dioxide and magnesium stearate, those are all a part of the structure that is the is the granule; is that correct?

A. As I reviewed the process before, yes, these are the three ingredients in the granule. I don't think Zydus uses any binders, at least not evident here.

Q. And --

THE COURT: I want to make it's used in the context of that sentence, the word "structure."

So, Dr. Sinko, is the structure that is part of the agreed upon structure, the construction the parties agreed on for the word matrix, macroscopically homogeneous structure. When he inserts the word structure in that question and references a granule, I want to make sure I understand you.

Is the granule the structure that you are looking to when you speak about a macroscopically homogeneous structure in all its volume? Is the granule the structure that's referenced in that definition matrix or not, if you can answer that?

THE WITNESS: Well, it's my opinion that it's distribution in the granule. Mr. Peterka before used the word "structure" for the granule and I asked what the

context was.

THE COURT: Yes. That's why I'm trying to be careful because I want to know what your opinion is about -- he may have something else, and I'm not suggesting he's doing anything he ought not to be doing, nor am I suggesting you are doing anything you ought not to be doing.

But the question I'm asking you: I hear the word "structure" in the context of this discussion about matrix. I'm asking myself what does structure refer to in the agreed-upon construction in the word matrix? What is the structure in the phrase, a macroscopically homogeneous structure in all its volume?

So I'm just asking you: Is the structure in that phrase as you look at the Zydus product that you have been called upon to opine about, is the structure the granules that you've been referring to that we've been talking about that are referenced on the exhibit that you helped create as a demonstrative? That's my question.

THE WITNESS: And my answer is the three-dimensional distribution, lipophilic of that magnesium stearate. And it is within the granule, but it's the distribution that is the structure -- I don't believe you necessarily need a physically interconnected structure that Mr. Peterka was talking about. It's the distribution within that structure that creates the volume.

THE COURT: So you are saying the granule is not the structure. It's the existence of the magnesium stearate in some --

THE WITNESS: Distribution.

THE COURT: -- in some chemical way that itself creates a structure? Am I hearing you right?

THE WITNESS: That's correct.

THE COURT: All right. Go ahead, Mr. Peterka.

MR. PETERKA: And I would just like -- if you don't mind, Your Honor, I'd just like to follow up on one thing you just asked.

THE COURT: Yes.

BY MR. PETERKA:

Q. You mentioned self-creates a structure, but that structure you're referencing, Judge Jordan asked you if it self creates a structure, and you said yes. Right?

THE COURT: I'm not sure I said that.

THE WITNESS: I'm not sure.

THE COURT: I think what I asked --

MR. PETERKA: I honestly --

THE COURT: I think you might have misheard me.

MR. PETERKA: But I may have, so...

THE COURT: Please don't make me try to say it again.

MR. PETERKA: Okay. I won't. I won't.

THE COURT: I've asked it as best I could. I've gotten an answer. I think I understand what he's saying.

MR. PETERKA: Okay.

THE COURT: It's up to you guys to persuade me one way or another whether it is a good or bad answer in the context of infringement, but I think I understand what he is saying.

MR. PETERKA: Got it.

BY MR. PETERKA:

Q. So turning now, I guess, to the volume that you contend the magnesium stearate particles make up in the granule; right? We're clear what we're talking about now?

A. The volume, the distribution volume of magnesium stearate?

Q. Yes.

A. Correct.

Q. Colloidal silicon dioxide is present in that volume; is that correct?

A. In my opinion, it depends on how you refer to volume, but if you are talking about the matrix, the matrix is the magnesium stearate. If you are talking about colloidal silicon dioxide in the granule, yes, it's in a granule, but it does not have an effect on the lipophilic character, and so to me, it's unrelated.

Q. Well, I'm asking you -- I will try it again. I will

pull out the deposition if we have to. But within that volume that you contend the magnesium stearate makes up in the granule, colloidal silicon dioxide is present in that volume; is that correct?

A. Are you asking if colloidal silicon dioxide is in the matrix?

Q. I think my -- was my question unclear? No.

A. Yes, it was unclear to me.

Q. The volume that you contend the magnesium stearate makes up in the granule, is colloidal silicon dioxide present in that volume?

A. Well, to me, if colloidal silicon dioxide is used to be, you know, in the volume, in the matrix or not, the properties are not -- the lipophilic properties won't be affected, so that's why I keep saying it's unrelated.

To me, as a scientist, okay, as a scientist, you know, magnesium stearate is a potent lipophilic, and colloidal silicon dioxide is considered hydrophilic. In the context of the patent, it's very weak hydrophilic.

Q. Right.

A. So is it part of the volume in the matrix? It's in the granule, but it is not going to have any effect.

Q. Right. You're still not answering my question.

A. All right.

Q. You understand -- are you asserting that there's a

volume of magnesium stearate though, is that right, in the granule?

A. That's right. In three-dimensional distribution, magnesium stearate makes the inner matrix.

Q. Within that volume, we understand what volume is; is that right? There's colloidal silicon dioxide in that volume; right?

A. Well, if you're -- if you are saying that the colloidal silicon dioxide is in the matrix, like I said --

Q. I'm asking a pretty clear question, I think. I'm asking: Is it in the volume --

A. Is it in the volume of the granule?

THE COURT: No. I think what he's asking -- and I do think it's pretty clear, I will ask it again, Dr. Sinko.

THE WITNESS: Okay. Sure.

THE COURT: You said that the magnesium stearate in itself creates a volume within the granule, and the volume that the magnesium stearate creates, that is the matrix. If I understand you right, that's what you've said.

He's asking, is this other excipient within that volume, that volume happens to be inside a granule or it's not inside the granule, does that set of magnesium stearate

molecules constitutes a matrix, is this other excipient in there, too? I think that what he's asking. That's what you need to answer.

THE WITNESS: Okay. I think it's physically within the volume. I guess I wouldn't think -- I would not -- I was not trying not to answer. I just think I misunderstood.

THE COURT: Well, I think you keep saying, well, that's irrelevant, but that's really, with all due respect, that's not your judgment to make whether it's relevant or not. He's asking a question of fact, is it in there or is it not in there? If you can answer that question, you need to answer it, and then we'll let these guys argue about whether it's relevant or not. Okay?

THE WITNESS: Sure.

THE COURT: We'll let them battle that out. And I'm sure that Mr. Lief is going to get up and ask you some questions on redirect, and you'll have a full opportunity to explain why you don't think it's relevant, and your explanation may be the most relevant thing of all. But please answer that question, that question about whether this other excipient is in that matrix as you've defined it consisting of the volume of magnesium stearate.

THE WITNESS: So I would say that it is within the matrix.

THE COURT: Okay. You got your question. Let's move on.

MR. PETERKA: Thank you, Your Honor.

BY MR. PETERKA:

Q. And mesalamine is also in that volume; is that correct?

A. And I would, based on that, I would say the same thing, mesalamine would also be in that.

Q. Colloidal silicon dioxide is hydrophilic; is that correct?

A. Well, not within the context of the patent. As I described, hydrophilic has certain properties, and actually, if you recall from yesterday, Mr. Kulkarni actually said that it was not, there's no hydrophilic in those first compacted -- no hydrophilic excipients in the compacted granules. It's a porization element. You know, but it does not swell and have that kind of property.

Q. Did you listen to the last part of Mr. Kulkarni's deposition, where he corrected that testimony?

A. Yes, I did. I don't recall specifically what it was, but if you want --

Q. Where he said it was hydrophilic? Did you hear that?

A. You mean when -- when Zydus' counsel asked the question a second time? I mean asked the question?

Q. Yes.
A. Yes, I did hear that, but I think his -- his first answer, he says, look at the '720 patent, and you look at the way they define hydrophilic.
Hydrophilic, it talks about viscosity increasing and swelling, and it's just like microcrystalline cellulose. It attracts water, but it does not swell to a much greater volume. And I think his first answer was -- well, I can't give it, but it might be technically hydrophilic, but not with the content of the patent.
Q. So hydrophilic has been construed as having an affinity for water. You're familiar with that; is that right?
A. That's correct.
Q. In the context of the '720 patent; right?
A. That's correct.
Q. So colloidal silicon dioxide is hydrophilic under that definition; is that correct?
A. It has an affinity for water, but it does not swell.
Q. Colloidal silicon dioxide gels when exposed to water; correct?
A. You may be able to call it gelling. I'm not sure you've ever seen it. If you take colloidal silicon dioxide and add water to it, it makes little pellets, almost like

Chia seeds, and you could pour them out. So it's like a very, like, low viscosity type gel, and that's why I made the distinction. But does it have an affinity for water? Yes, technically, it does.

Q. And it does gel, at least to some degree; is that right?

A. It gels to some degree, but not to the degree where it would have the ability to impede water flow, which is the context of the '720 patent.

Q. You would agree with me that colloidal silicon dioxide can act as a porization element; is that correct?

A. Yes, I've seen that.

Q. And the '720 patent actually talks about compositions in the background of the invention section where they use colloidal silicon dioxide as a porization element; is that right?

A. Yes. In fact, I pointed out one of the passages.

Q. Right. Now, that passage was from the background of the invention; is that right?

A. Yes, it was.

Q. And the way a porization element works is it associates with water, which then dissolves the material leaving a pore, which allows more fluid to flow through that pore; is that correct?

A. Well, that brings up -- actually, you bring up a key

distinction. It associates with water and it dissolves rapidly. By dissolving rapidly, it creates a pore whereby more fluid could flow whereas the hydrophilic compounds that the patent discusses form these hydrogels that stay intact and form a resistance to other water flow, because it prevents water from flowing through it because it's very viscous or thick, whereas the porization element, it's meant to dissolve very rapidly and leave a hole, and so it would not offer much resistance, and that's the distinction I've been trying to make.

Q. So a porization element increases the amount of fluid that is able to permeate a structure in which it is present; is that correct?

A. Well, it creates a pore. And depending on the formulation, you know, it could do that.

Q. I want to talk to you about the word "macroscopic" in the construction of the claim term matrix. You are aware that term is in the construction; is that right?

A. Yes, I am.

Q. All right. The macroscopically homogeneous, homogeneous structure?

A. Right.

Q. You would agree with me that macroscopic means large enough to be viewed with the naked eye; is that correct?

A. Well, I think that's, that's one definition.
Q. Do you recall your first expert report in this case? I know we looked at one of your earlier ones a little bit ago, but do you recall the very first one you submitted? That may have actually been that one.
A. I mean, I've reviewed the report.
Q. If you could go to your -- it's your ...
(Pause.)
MR. PETERKA: Your Honor, may I approach again?
THE COURT: Yes, you may.
(Mr. Peterka hands exhibits to the Court.)
MR. PETERKA: May I approach the witness?
THE COURT: Yes.
(Mr. Peterka handed an exhibit to the witness.)
BY MR. PETERKA:
Q. If you could turn to, I think it's your first report. Yes. January 9th, 2012 report and I think it's the first tab in that binder, that book. Go to paragraph 57.
Do you see there, you say, "I also reviewed dictionaries to confirm my understanding of the meaning of the words 'macroscopic' and 'homogeneous'"?
A. Yes, I do.
Q. And you say, "According to the Merriam-Webster's Dictionary, macroscopic means large enough to be observed by the naked eye and involves large units or elements."

A. Yes, I see that.
Q. Do you disagree with that definition of macroscopic?
A. No. I mean, that's a -- that's a definition that I state here.
Q. That's a definition you stated in this section of your report opining on how these terms should be construed; is that right?
A. Yes.
Q. So back to my earlier question: You would agree with me that macroscopic means large enough to be viewed with the naked eye; is that correct?
A. Macroscopic is, you can view it with a naked eye, but it does not mean -- you have to -- I think we've had the discussion during depositions. It depends on what you're looking at; right?

I could be looking at a tablet. I could be looking at a picture of a piece of a tablet and I think, you know, that it could be used in a variety of ways, but, yes, it's using your eye. You're looking at something, and depending on how you focused, you may have to focus just with just your eyes, or you may be able to focus with the aid of something else, where you can zoom in on an area and look with some sort of, you know -- you've seen sort of pictures or something. But it's with respect to what you observe with your eyes. That's correct.

Q. So like with a microscope?
A. Well, if you, if you're -- if you're looking through a microscope, you are still, you're still seeing, you are still seeing a view of the area, and, you know, I have used the word "macroscopic" with -- in, you know, my thesis research, for example. Macroscopic mass balance approach.

It's the -- it's the view, whatever frame you're taking being, like I said, you know, a tablet or zooming out of a tablet, or my other case -- sorry, case. But in the situation I'm talking about with the thesis, I was looking at the intestine or part of the intestine, and so it's how you look at that and look at that, that area or zone that you're, that you're focusing on.

Q. So it's your testimony that macroscopic includes viewing things in a microscope? Is that your testimony?
A. Well, my testimony is that you, you're looking at something, right, and when you are -- and, you know, if -- if it's large enough to be observed by the naked eye.

So, I mean, if I'm looking at a zoomed-in picture, it's large enough for me to observe by the naked eye. If I'm looking at -- well, even if I look at a cross-section of a tablet, I may have to take out a magnifying glass to look at it, but I could still with my eyes determine that. Right? I mean, tablets are quite small. I could zoom in even further and look at a picture

as part of the tablet.

Q. All right. So just to be clear, I want to make sure I understand. You're now departing from your view that was expressed in paragraph 57 of your initial expert report, and you are saying viewed by the naked eye means viewed by the naked eye with the assistance of a magnifying glass or a microscope. Is that what you are saying?

A. I'm saying it's large enough to be observed by the naked eye.

Q. So can you answer my question? If you need a microscope or a magnifying glass to view something, are you viewing it with your naked eye?

A. That's the way I -- that's the way I use it, because if I can view it with my eye, that's the -- I think during our depositions, I've talked about point of reference, zooming and zooming out. If I can view it with my eye and I can determine it, then, yes.

Q. You never observed with your naked eye whether the ingredients in the Zydus compacted API -- let me strike that, back up.

You never observed with your naked eye whether the ingredients in the Zydus compacted mesalamine granules that you contend are there, whether those ingredients are homogeneous, did you?

A. I've never handled that tablet. I've just been --

pictures that we've saw yesterday of the, of the intact tablet.

Q. Okay. So as far as you're aware, none of the experts for Shire have observed with the naked eye whether the ingredients in the Zydus compacted mesalamine granules are homogeneous; is that correct?

A. Well, Dr. Davies did do mesalamine chemical imaging, and so, you know, that would be homogeneous, and that would be -- that would include the two matrices.

Q. Now, Dr. Davies only looked for mesalamine though; right?

A. Well, that's true, but you asked about homogeneous, and I'm just trying to say, I mean, that's one indication. And like I said before during my direct, you know, the mixing steps, you know, would show that, you know, that these processes are resulting in a homogeneous mixture. Otherwise, you would have an unreliable product and you would not submit that to the FDA.

Q. So the answer to the question I'm hearing is, no, none of Shire's experts have observed with the naked eye whether the three ingredients in the Zydus compacted mesalamine granules, which would be mesalamine, colloidal silicon dioxide and magnesium stearate, whether those three ingredients are homogeneous; right?

A. I think I answered the question that Dr. Davies

showed mesalamine being homogeneous, and since the tablet is made up of a vast majority of mesalamine in those granules, it would be.

Q. So only mesalamine, that's the only thing you were looking for?

A. As far as I know, Dr. Davies only looked for mesalamine.

Q. Even if you tried, you probably couldn't observe distribution -- let me strike that.

Even if you tried, you couldn't observe the distribution of those three ingredients in the Zydus compacted granules with your naked eye, could you?

A. So I mean, I didn't try to do that. You know, different ingredients, you know, do have different, you know, shades of color. That might be possible. But I didn't try to do that.

Q. And as far as you're aware, none of the other experts in the case did either; right?

A. Well, as I said, Dr. Davies did with mesalamine. But I'm not aware of any of the others.

Q. I want to talk to you -- well, actually, let me go somewhere else here.

On the topic of Dr. Davies' testimony or his, I guess his testimony here, Dr. Davies' testing did not show the location of any excipients in the area to be analyzed;

is that right?
A. That's different than the question you just asked me. I think he only looked at mesalamine.
Q. And he did not show mesalamine was associated with magnesium stearate in a particular region of the, of the cross-section; is that correct?
A. I think he just looked at mesalamine.
Q. And he did not show if mesalamine was associated with any other excipients anywhere in the tablet; is that right?
A. I think he just looked at mesalamine.
Q. In your original expert report in this case, your opinion was that the Zydus ANDA product satisfied the are requirement -- let me back up. Let me just put this in context.

I'm going to talk to you a little bit about that requirement that the API, the mesalamine, be dispersed both in an inner lipophilic matrix and in an outer hydrophilic matrix. Okay?
A. Okay.
Q. I think we looked at that term a little earlier. In your original expert report in this case --

MR. PETERKA: Actually, can I get the patent? Just DTX-1. Go to the claims. It is the very end of claim 1. There we go.

BY MR. PETERKA:

Q. "Wherein the active is dispersed both in the lipophilic and the hydrophilic." Just so we're all clear, that's what we're talking about.

A. Okay.

Q. In your original expert report in this case you opined, your opinion was that the Zydus ANDA product satisfied the requirement that API be dispersed in both matrices because API, or mesalamine, was dispersed in an inner lipophilic matrix which was in turn dispersed within an outer hydrophilic matrix.

Is that correct?

A. Can you just point me to that section?

Q. Sure. Well, you know, why don't we go to the deposition. It's a little easier.

MR. PETERKA: May I have the 2014 deposition? If you go to page 283.

THE WITNESS: So which one?

BY MR. PETERKA:

Q. The 2014 deposition. Go to page 283, lines 14 through 23.

A. That is the 1/12 Sinko transcript?

Q. Yes.

A. What page?

THE COURT: 283.

BY MR. PETERKA:

Q. 283. If you go to lines 14 through 23, I asked:

In your original report, your opinion was that there was -- the Zydus ANDA product satisfied the requirement that mesalamine be dispersed in both the inner matrix and the outer matrix.

You said that was satisfied because mesalamine was dispersed in an inner lipophilic matrix, which was in turn dispersed within a hydrophilic matrix; correct?

And you answered, correct.

Did I read that correctly?

A. Yes, you did.

Q. And in your original expert report in this case, you did not include any mesalamine -- strike that. In your original report, you did not include any opinions that it was mesalamine separate from what had already been incorporated into an inner lipophilic matrix that was subsequently incorporated into an outer hydrophilic matrix; is that correct?

A. Yes, I think so.

Q. And, in fact, in your first deposition after you submitted that report, you testified that you had no evidence that there was any mesalamine in the final ANDA product that was not part of the alleged inner lipophilic

matrix; is that correct?
A. Can you please repeat that question?
Q. At your first deposition in this case, which was in 2012, after you submitted your very first report or your very first series of reports, you testified that you had no evidence at that time --- let me strike that. Back up.
At your first deposition after you submitted -- after the first round of expert reports in this case, you testified that you had no evidence that there was any mesalamine in the final ANDA product that was not part of the alleged inner lipophilic matrix; is that correct?
A. Once again, can you just point me to that -- to that part?
Q. Yes. I can take --
MR. PETERKA: Can we go to the 2012 deposition, which is -- it's the first Sinko transcript in there at page 10 and lines 14 all the way to the bottom. Actually, all the way over to 311. Actually, wait. To 311, 3. The 310, 14, to 311, 3.
BY MR. PETERKA:
Q. I said that you don't know -- are you there? Are you there?
A. Yes. You mean in the line 14 and on page 310 spanning?

Q. Yes. Over to the top of page 311.

I said: But you don't know for a fact that there is API that is not within that inner lipophilic matrix that's also put into the -- that ends up in the outer hydrophilic matrix; right?

You said, well, what I just said is, I will skip that. The intent is to make the inner lipophilic matrix, I have to assume that's what they did. If there's a small amount that did not get in there, I can't tell you that.

Did I read that correctly?

THE COURT: Well, not entirely, because you substituted the word "did" for "made."

MR. PETERKA: I'm sorry.

THE COURT: I don't know that you have to read it again. He has it in front of him. If you want to ask him whether that's his testimony?

MR. PETERKA: Yes.

BY MR. PETERKA:

Q. Okay. Was that your testimony? Do you want me to reread it?

A. Well, I mean, this is what I said.

Q. Okay. You said, if there's -- the essence was that there's a small amount of mesalamine that did not get into the inner lipophilic matrix that you said was there. If there was a small amount of that did not get into that inner

lipophilic matrix, you couldn't tell me that; right?
A. And at the time of this deposition, you know, I had not contemplated that, but, of course, this had been going on for quite awhile and as I kept thinking about the processes, you know, my thinking, you know, got more in depth, and so at this point, you know, I just said I had not contemplated that.
Q. At the time you submitted the report that we were discussing at that deposition, you were aware of the manufacturing process for the Zydus ANDA product; is that correct?
A. Yes, I was.
Q. And you were aware of the type of equipment that was used in that process?
A. Yes, I was.
Q. Including the fact that roller compaction was used?
A. Yes. Roller compaction is a smaller --
Q. You were aware that Zydus was using roller compaction in its process?
A. That's correct.
Q. And you were aware of the ingredients going into that roller compaction?
A. Yes. I reviewed the ANDA.
Q. And you were aware that fines could be generated by roller compaction at the time you submitted your first

report; right?
A. That's correct.
Q. There's no reason you couldn't have included that opinion in your first report, is there?
A. No. At the time, I didn't.
Q. I'd just like to talk to you a little bit about your opinion on the fines that you have come up with since that time.

Fines are just small particles that can be generated during the manufacturing process; is that correct?
A. Fines are -- fine particles are produced during the manufacturing process, as I stated in my direct. And, in particular, fines, you know, are produced from the different granulations, and they're an important part of the formulation typically in making a cohesive tablet.
Q. And maybe I -- so the fines were just smaller particles that are generated, not processed, right, in the manufacturing process?
A. Fines are small particles below a certain size.
Q. All right. And fines can be thick -- sorry.

Fines can be smaller versions of granules; is that correct?
A. I think it's fair to say that fines are, could be fine particles of the excipients, of the active ingredient, and a small granule. It's going to be some mixture.

Q. You don't know the percentage of fines that are generated in the Zydus manufacturing process, do you?
A. I couldn't find an exact number, but typically, you know, with the granulation process, it's in the neighborhood of 15 percent, plus or minus.
Q. So you don't know what that amount is, the amount of fines that is generated in the Zydus process; right?
A. I don't recall seeing that.
Q. And you also don't know what amount of those -- let's talk about the fines that you -- take a step back here.

I want to talk a little bit about the fines that you think are there, but you can't really tell me how many are there. I want to talk about what those fines might be. Okay?
A. Sure, but I don't agree with your characterization. Like I said, I mean, from the process, I know there are fines. Typically, it's in the range of 15 percent. Zydus did not use a binder, so it's could be in the higher range of 15, 20 percent. Like I said, I did not see a specific number.
Q. So of those alleged fines, you don't know -- you don't know the amount of those fines in the Zydus manufacturing process that are pure mesalamine, do you?
A. It is going to be some distribution. I -- I did not see the analysis of fines. But the product is, you know, is

a very high fraction of the mesalamine, so it's likely that, you know, the majority of the plain particles would be mesalamine in my opinion.

Q. You weren't provided with any data that would allow you to determine the percentage of fines that are pure API, pure mesalamine; right?

A. Well, I think as, as I've stated, I don't recall seeing data of fines, an analysis of it, but understanding the process, you know, it would suggest to me that the fine particles probably would be mostly mesalamine, mostly mesalamine, you know, in the product.

Q. And, in fact, you would be guessing if you tried to tell me the amount of fine in the Zydus manufacturing process that are pure mesalamine; is that correct?

A. Well, I think you have to go -- you have to go back to what is a, what is a granule. Right? A granule, you aggregate material together, and so when you get to a certain, you know, particle size, you're going to have this, you know, free mesalamine particle.

So is it a guess? I guess it's an educated guess based on my experience and understanding the way these processes work.

Q. So it's a guess?

A. I think it's a, it's -- it's an educated estimate, if you want to put a time point on it.

MR. PETERKA: Can we go back to the 2014 deposition? And this is at page 292 to 293. I have 292, 22, through 293, 17.

BY MR. PETERKA:

Q. Mr. Kulkarni's deposition testimony is the only support you have for your opinion that there are some fines in the manufacturing process that appear to the eye? He said, no, I disagree. I also looked at the roller compaction process.

And it would just, once again, make sense if you're looking at probability, what's probable, what's likely, it's likely that you're going to have some pure API, some smaller granules. I'm not provided any data to make that assessment, so I wouldn't want to guess. Like I said, it could be 50/50, it could be something else. It would be a guess.

Did I read that correctly?

A. Yes, and I think that, you know, is consistent with what I just said. I said, you know, it's an estimate. It's -- you know, you have to -- you know, you asked me if I knew. I had not seen any data. That's where we started. Right? But this is not -- I mean, to me, this is not any different. I mean, there's going to be free mesalamine fine particles in there, and it could be 50/50, but the point is it's free mesalamine particles. And if you are talking

about 15 or so percent of the total blend, you know, it's still a significant amount.

Q. You did not do any analysis of the fines that you contend are in the Zydus product to determine their composition, did you?

A. I did not have access to any raw materials or intermediate materials or the final tablet. I just have gone by, you know, my experience and my understanding of these processes and how they work.

Q. And none of Shire's other experts, as far as you're aware, did any analysis of the fines that you contend are in the Zydus ANDA product to determine their composition, did they?

A. Not that I'm aware of.

Q. I want to talk a little bit about Dr. Hoag's tests that you referred to earlier today.

Did Dr. Hoag use the same -- do you know if Dr. Hoag used the same materials that are used in the Zydus compaction step?

A. Yes, I think he used mesalamine, magnesium stearate and colloidal silicon dioxide.

Q. Did he use the same grades of mesalamine, magnesium stearate and colloidal silicon dioxide that are in the compaction test?

A. You know, I'm -- I am generally aware there was some issue, but I don't recall specifically. But at the time I

saw it, it did not strike me as necessarily significant, but if you would like to review it, sure.

Q. So he may have used different grades of material; right?

A. He may have.

Q. If we could go to Dr. Hoag's report, I think it is in your binder. It's at paragraph 37.

A. Sorry.

Q. Sorry.

A. Which tab?

THE COURT: After the transcripts.

MR. PETERKA: The very last.

THE WITNESS: Okay.

BY MR. PETERKA:

Q. Could you go to paragraph 37 in Dr. Hoag's report. He has got a table there with a blue heading.

Do you see that?

A. In paragraph -- the top of page 9?

Q. Yes, the top of page 9?

A. Yes, I see it.

Q. These are the bulk densities for the granules of colloidal silicon dioxide and magnesium stearate and the bulk densities of pure mesalamine granules?

Do you see that?

A. Yes, I do.

Q. Well, the bulk density, he made three of each, and for the blended, the one with colloidal silicon dioxide and magnesium stearate, the first one was .297 grams per millimeter, the second one was .308, and the last one was .3; right?

A. Yes. With an average of .302.

Q. All right. And if you could go back to DTX-18, which is the Zydus batch record. And if you could go to page 235700.

And actually, the next page, 235701. Do you see there's a bulk density determination in the batch record?

A. 235700.

Q. 701.

A. Yes, I do.

Q. And do you see there that it says bulk density determination, and it has some instructions there. At the very bottom it says, if the average bulk density is less than 0.40 grams per milliliter, repeat cycles of step 6.3.1 to 6.4.1 till desired bulk density is achieved and then stop the process.

Do you see that?

A. Yes, I do.

Q. And then 6.3.1 is on the previous page. That's the -- that's the raw compaction or sizing process; is that correct?

A. Yes, it is.
Q. All right. So the batch record says that if the bulk density of the compacted mesalamine with the colloidal silicon and magnesium stearate, if the bulk density is less than four, you're supposed to roll compact it again until you get to .4; is that right?
A. For the Zydus ANDA product, your specification has to be less than .4. That's correct.
Q. Less than -- okay.
THE COURT: I'm not --
MR. PETERKA: No. It's greater than .4.
THE WITNESS: I'm sorry. Greater than 4.
BY MR. PETERKA:
Q. Right?
A. Sorry. Yes.
Q. So if it's less than .4, you compact the granule -- strike that. I'm sorry.
If you compact the API and the colloidal silica and the magnesium stearate and you get a bulk density that is less than .4 it would tell you to go back and do it again?
A. For the Zydus ANDA product, that's correct.
Q. So Dr. Hoag, his granules with colloidal silicon dioxide and magnesium stearate that have an average bulk density of .302, they could not be used in the ANDA product;

is that correct?

A. So at least I think that you're missing an important part or point to this test. He's comparing in his test the pure mesalamine versus the ingredients that are in the inner granule, and you see the bulk density is very similar, and so he's just looking at the relative penetration. You have to hold, you know, all of the other parameters constant, and he held the bulk density constant here, you know.

Could he have held it, you know, at, you know, greater than .4? He could have. You have to ask him, but the point is that these parameters are constant, and so you're -- you're testing, you know, something that's equal.

Q. So you did not answer my question then. So with a material that had a bulk density of .3, right, all right, you couldn't, you couldn't use that -- he couldn't go forward in the Zydus batch record if he had a bulk density of .3. You would have to go back and lower compact it again; right?

A. If you're, if you're making the Zydus ANDA product, that would be true, but that's different than the test he is showing he's trying -- he's holding parameters constant. And so he's -- I guess the word would be he used control for that.

Q. And you would agree with me that at no point in the manufacturing of the Zydus ANDA product does Zydus compress

its roll compacted mesalamine into a compact; right?
A. Well, the step is called compaction.
Q. But at no point does Zydus take the material that comes out of that compaction step and compress it into like a, whatever shape of the material Dr. Hoag, that he called, when I'm talking about compact -- I'm referring to what Dr. Hoag referred to as compact. There are images of them in here in his report on page 12.
A. Sure. Well, what comes out of the compaction process of Zydus, that first granulation step, are these certain, certain size, and they're -- they're also, you know, compacted versions of the ingredients. These are just compacted into a version that looks like a, you know, a disk, or maybe a small tablet.
Q. And then at no point within the manufacture of the Zydus ANDA product does Zydus take the material that comes out the roller compactor and make it into a shape like this; right?
A. No, they don't make it into the shape. They size them into a certain size granule so they can make a second granulation.
Q. In forming your opinions in this case, you reviewed the conclusions of Dr. Hoag in his expert report; correct?
THE COURT: Hold on just a second.
Let me ask a question or two for a minute.

MR. PETERKA: Certainly.

THE COURT: Will the difference in bulk density, if you know -- you know what? I apologize. You go ahead, Mr. Peterka.

THE WITNESS: I can answer that question.

THE COURT: I think you know where that is going. I'm sure Mr. Lief will ask it.

THE WITNESS: Okay.

BY MR. PETERKA:

Q. In forming your opinions in this case, you reviewed the conclusions of Dr. Hoag in his expert report; correct?

A. Yes, I did.

Q. And in his expert report, Dr. Hoag concluded that the granule that he created simulate the inner volume of the granules, sorry, of the Zydus ANDA product; is that right?

A. Yes, I think compositionally they simulate the inner granules of Zydus's ANDA product.

Q. And based on Dr. Hoag's report, you also concluded in your report that the blended mesalamine compacts are representative of the products from the Zydus dry granulation step; right?

A. Yes. And, you know, I believe that. I think that Dr. Hoag did a great test. He held primers constant and he looked at the critical variables that were different.

Q. You were present yesterday when Dr. Hoag testified;

right?
A. Yes, I was.
Q. And you heard Dr. Hoag testify that he was not offering an opinion that the granules he created simulate the inner volume of the Zydus ANDA product; correct?
A. Yes, I heard him say that.
Q. So that although Dr. Hoag, the person who made the granules, has abandoned his opinion that the granules he created simulated the inner volume of the Zydus ANDA product, you are still sticking with that opinion?
A. So you say he abandoned the opinion saying he changed his mind?
Q. He testified yesterday he was not offering an opinion that the granules he created simulated the inner volume of the Zydus ANDA product.
A. Right. So how did he abandon the opinion?
Q. Well, that was an opinion he had in his original report?
A. Okay.
Q. In his report, he said, he concluded that the granules he created simulated the inner volume of the Zydus ANDA product. And then yesterday, when he was asked if they did that, he said he was not offering that opinion. Right?
A. I heard him. I heard him say that yesterday.

Q. So although he, Dr. Hoag, who made those granules, is abandoning that opinion that they simulate the inner volume of the Zydus ANDA product, you're still onboard with that?
A. I'm still, I'm still onboard because it has the materials and the same amounts. They're compressed. And for a drug like mesalamine which is reasonably high solubility, the compaction, that density is not really relevant.

If it was a low solubility drug, then the difference in that bulk density may concern me but not for mesalamine. He held the primer constant. Mesalamine is a reasonably high solubility drug. I wouldn't expect that bulk density measurement to make a significant impact. And so I think it does simulate.

Q. I want to talk a little bit about your function-way-result test that we talked about earlier for the, I think it was for the magnesium stearate. Right?
A. Okay. I don't recall discussing it with you, but ...
Q. That's fair. We did not discuss it. You discussed it with your attorney.
A. Okay.
Q. I think you identified the function of the, I think you were comparing it to stearic acid; is that right?
A. I was comparing magnesium stearate to stearic acid.
Q. I think you identified the function of stearic acid

in the patent claims as controlling release?

A. Can we have just put up my slide?

Q. Sure. Yes, sure. I think it's PDX-8.11.

So the function in the function-way-result is controlling release; right?

A. Controlling release as an inner lipophilic matrix, that's correct.

Q. Now, if you could go to, in your binder there, or I'm sorry, in the spiral bound thing with your reports, if you go to your February 3rd, 2012 report, at paragraph 12. It's on page 6.

A. Paragraph 12?

Q. Yes, paragraph 12.

A. Yes, I see it.

Q. And about four lines down, it says it says the '720 patent specification never suggests that the inner lipophilic matrix should be defined to "control the release of the active ingredient from the dosage form."

Is that right?

A. Let me just read it.

So if I recall correctly, I mean at this point in time, I mean this situation, and I'm not a patent attorney, but the situation was different. I'm not sure if everything was defined at this point in time. And this is, yes, this is one of the earlier reports. But that is what

I state. I mean at this snapshot in time.

Q. Okay. So that function that you say, the '720 -- actually, strike that.

THE COURT: Mr. Peterka?

MR. PETERKA: I think that is it. Yes, that's all I have.

THE COURT: All right.

MR. PETERKA: Thanks. Thanks, Dr. Sinko.

THE COURT: Dr. Sinko, we'll see if Mr. Lief has any questions.

REDIRECT EXAMINATION

BY MR. LIEF:

Q. Dr. Sinko, with respect to Dr. Hoag's test, in your opinion, are the two things that he compared, do they have similar bulk densities?

A. Yes. As I stated earlier, that's one of the factors that was kept constant between the two. And so those two parameters were kept constant and therefore they're similar.

Q. And in your opinion, would any difference as between the Zydus bulk density and the bulk densities of those two materials tested in Dr. Hoag's test have any substantial or any affect on the lipophilicity?

A. No. And, once again, as I stated here at the end of Mr. Peterka's cross-examination, you know, I would, on a

drug like mesalamine, I would not expect that. It was a low solubility drug. There is some literature evidence about that, but I would not expect that from this.

Q. And the results of Dr. Hoag's test showing that the material containing the magnesium stearate took water in slower than the pure mesalamine, are those results consistent or inconsistent with the other evidence that you discussed on direct regarding magnesium stearate slowing the release of mesalamine from various formulations that Zydus had tried?

A. They are consistent.

Q. Is there anything that you heard in Mr. Peterka's cross-examination of you that would lead you to change your opinion that the inner lipophilic matrix is indeed lipophilic in character?

A. No.

Q. There was some discussion of the word "macroscopic." I don't want to do a legal analysis with you, but I'd like to look, if we could, at PDX-8.4.

And the agreed upon construction of "matrix" is "a macroscopically homogeneous structure in all its volume."

Now, "its." There was discussion about "its."

A. Yes.

Q. Now, I want you to assume for this question that the "its" is a very small volume, a volume that cannot be seen

by the naked eye. "A homogeneous structure in all its volume." Let's say we had a very small granule, for instance. Would that change your view of "macroscopically homogeneous?"

A. No, it would not.

Q. And if you assumed that a legal definition were imposed on you that "macroscopically" means "throughout that volume," okay? Take that assumption for the product we've been talking about.

MR. PETERKA: I'm going to be object. This is outside the scope of the direct and the cross.

THE COURT: Well --

MR. PETERKA: I don't see what legal definition he is talking about.

THE COURT: He is talking about this, and I don't think he has to assume. That is the definition we're working off of. Your objection is overruled. You can go ahead and ask the question. Let's go ahead and get it done.

BY MR. LIEF:

Q. All right. Assuming that legally "macroscopically" would mean "throughout." Is the magnesium stearate in the inner region of the Zydus granule macroscopically -- well, forget macroscopically. Is it homogeneous throughout that granule?

A. Yes, it is.

Q. And in terms of all three chemicals that are in there, the mesalamine, the magnesium stearate, and the colloidal silicon dioxide, are all of them, taken together, homogeneous throughout that region?

A. Yes, they are.

THE COURT: Now I'll ask a question, Mr. Lief.

What does the word "macroscopically" add to that definition? You're a scientist. What meaning does it have in there to you?

THE WITNESS: So as a scientist, "macroscopic" to me means you're looking at a -- it's the word "structure" now. But you are looking at something. You are focusing in on an item and you are looking at it throughout that, in this case, that volume or whatever it may be. And "macroscopically" means when you examine it, you are looking at, you consider it. You are considering the entire, I call it, zone before the entire item, entire volume.

THE COURT: Okay. Thanks. Go ahead, Mr. Lief.

BY MR. LIEF:

Q. There was some discussion about your earlier report and maybe your earlier deposition in 2012 in the four rounds and whether you had discussed the presence of mesalamine in the outer matrix. Do you recall that during cross-examination?

A. Yes, I do.

Q. Now, I'd like to show you, if we can, Mr. Kulkarni's

deposition of 2014.

Can we bring that up? And if we could look at pages 150 to 151.

MR. PETERKA: Can you give me one second just so I can catch up?

THE COURT: It's your clock, Mr. Peterka.

(Counsel confer.)

MR. PETERKA: Is this designated?

MR. LIEF: It is designated, but candidly I don't think it would matter.

MR. MILLER: What page and line?

MR. LIEF: I'm going to direct him to page 150, line 19 through 151, line 2.

THE COURT: Why don't you take it off the screen until we got this worked out. Thanks.

(Pause until Mr. Gaertner nods assent.)

THE COURT: Okay. Go ahead, Mr. Lief.

BY MR. LIEF:

Q. If we could put that back up. And I will read you the questions and answers. I believe this was played yesterday, if memory serves. But the question at line 19:

"Question: At the end of the Zydus process, in the compaction process where you do the roll compactor and the oscillating granulator, do you get particles of different sizes?

"Answer: Yes.

"Question: And do you get, amongst those particles sizes, what would be called, 'fines?'"

Going over to the next page.

"Answer: Yes."

Now, Dr. Sinko, at the time, this is a 2014 deposition. I think this is a fairly obvious question but at the time of your 2012 report, your 2012 deposition, I take it you didn't have this 2014 testimony in front of you from the formulator at Zydus commenting on his process?

A. No, I did not.

Q. Okay. And at the time of those 2012 reports and depositions, did you have Dr. Davies' Raman test showing the mesalamine as he showed it in his Raman pictures?

A. In 2012?

Q. Right.

A. Yes, I think so. I don't remember. I didn't realize it.

Q. That's fine.

A. So the answer is yes.

Q. The record will reflect what it does about the timing of Dr. Davies.

A. Yes.

Q. The question is whether you know the amount of mesalamine that is in the fines, the percent of the fines

that are mesalamine and whether or not, and how much of it would be in the outer.

If we could look back at the claim for a minute, the PDX we had up earlier.

In the discussion here, at the bottom: Wherein the active ingredient is dispersed both in the lipophilic matrix and in the hydrophilic matrix.

Is there any mention in that claim of how much of the mesalamine should be dispersed?

A. No, there is not.

Q. Based upon anything you heard during cross-examination, do you have any reason to change your view as expressed during direct that mesalamine is present in both the inner matrix and the outer matrix?

A. No, I do not.

Q. I talked to you a little bit about colloidal silicon dioxide. If you look at element 1(b) in the various categories, the chemicals listed there, colloidal silicon dioxide, does it fall into any of the categories in 1(b)?

A. No, it does not.

Q. And, again, I think you answered this question before, but if the inner matrix were to be for some legal reason deemed to be inclusive of the colloidal silicon dioxide, in your view, would that inner matrix be lipophilic or not lipophilic in property?

A. It would still be lipophilic in property.
Q. Okay. And would the presence of that colloidal silicon dioxide in your view be related or unrelated to that lipophilic property?
A. Well, since it is lipophilic, I would say it would be unrelated.
MR. LIEF: Nothing further.
THE COURT: All right. Thank you, Mr. Lief.
Thank you, Dr. Sinko, for your testimony. You may step down, sir.
Mr. Haug.
MR. HAUG: Plaintiffs have no further witnesses. So subject only to making sure.
We have the right exhibits all in, I think we have been trying to do that but we would rest our case at that point.
THE COURT: All right then.
Subject to their confirming that the exhibits are in, I understand now plaintiffs rest. Do I have any applications?
MR. GAERTNER: Yes, Your Honor. It's Mike Gaertner on behalf of Zydus, the defendants.
The defendants at this time move for judgment as a matter of law pursuant to Federal Rule of Civil Procedure 52(c) because the plaintiffs have not presented a legally

sufficient evidentiary basis for a reasonable fact finder to find defendants liable for infringement, and I will list a few of those bases for Your Honor.

The first is we believe that the plaintiffs have not presented evidence of a macroscopically homogeneous structure in all its volume consisting of magnesium stearate.

In particular, we point to the testimony of Dr. Davies who has been able to locate any excipients in connection with mesalamine such that there is no scientific evidence to suggest that there is, assuming that magnesium stearate forms a matrix, that it is collocated with mesalamine such that you can show an analysis that the matrix exists.

The second thing is I think that you just heard on direct from Dr. Sinko that the dispersion, the theory that there is a dispersion of mesalamine within, I'm sorry, magnesium stearate within some greater volume, that dispersion not being continuous. That is not a structure. That is not a lipophilic structure such that mesalamine is then dispersed into this dispersion, which I don't quite understand is their theory, but I think it is pretty clear that that theory doesn't satisfy the Court's claim constructions in this case.

The next item we have, Your Honor, is that we believe that there is no evidence of an inner lipofillic matrix. You have already heard testimony that the granule

contains both lipophilic and hydrophilic excipients. The Federal Circuit was clear that you cannot have that. You cannot have a mixed matrix.

The second point is that the Hoag test does not establish that the granule, the alleged granule of the Zydus ANDA product has a lipophilic character. Dr. Hoag conceded that the test that he performed has never been published in a peer-reviewed article. Dr. Hoag does not offer an opinion that the material that he made simulates actually the Zydus ANDA product at all.

Dr. Hoag did not perform a drop penetration test, he admitted, as that test is recognized in the literature. Dr. Hoag can point to no other report where his test has ever been performed at all.

As he pointed out in the Mylan case, he performed different tests in connection with that.

Finally, Judge, we think there has been no evidence that mesalamine is sufficiently mixed to incorporate it with the inner lipophilic and the outer hydrophilic matrix, again, touching back to what we just heard from Dr. Sinko.

This dispersion of magnesium stearate in some greater volume, there is no testimony that is reasonable that one could conclude that those unconnected magnesium stearate particles that are in some undefined volume actually form a structure such that mesalamine has been dispersed within it.

THE COURT: Okay. Thank you, Mr. Gaertner.

Mr. Haug, do you want to respond?

MR. HAUG: My first response would be that as far as all the testimony that Your Honor has heard from the many experts, clearly, that becomes a question of fact, goes to the weight of the evidence. Your Honor will determine credibility as necessary and also give due weight or not to the testimony.

As far as the specific points that Mr. Gaertner had raised, whether -- I think he was saying that there is no evidence of a macroscopically homogeneous structure in all its volume. Clearly, there is. We have the manufacturing process. We have the fact that through that manufacturing process, mesalamine is mixed with magnesium stearate. It's mixed with colloidal silicon dioxide, sodium -- colloidal silicon dioxide. And we have testimony from Mr. Kulkarni, 30(b)(6) admissions, really, saying that the result of that process is to give a uniform mixture of magnesium stearate within that granule that is formed.

He said granules were formed. It was a uniform mixture of mesalamine, magnesium stearate, and as I said, sodium colloidal silicon dioxide.

And there's also testimony, fact testimony, binding testimony that none of that magnesium stearate leaks or leaves that granule.

We then have -- so Dr. Sinko just testified that the inner lipophilic matrix really is the magnesium stearate, which consists of a three-dimensional, three-dimensional distribution of magnesium stearate molecules within the granule. So you have to kind of close your eyes or not, but picture a three-dimensional structure within the granule, and it's homogeneous based on the testimony I just referred to by Mr. Kulkarni and also the expert testimony of Dr. Little, when he went through the process, saying what he thinks will result from that process and does result from that process.

In any event, you have this magnesium stearate which forms a macroscopically homogeneous structure. That's the three-dimensional distribution of magnesium stearate in all its volume. The volume, the testimony, the volume is the volume of the granule. The structure is the three-dimensional magnesium stearate distribution of molecules. That's the structure. That structure is in its volume. The volume is the granule. That's where it's captured, through the manufacturing process.

So, and the macroscopically homogeneous. I think it was a little confusing, but macroscopically, as is part of the agreed-upon term, I think a good example is, if you -- and if you look at your backyard and you look at the grass that you had planted in your backyard and you have

bare spots in it, is it homogeneous? Is it homogeneous from the standpoint of how you planted the grass?

Well, if you go to the bare spot, you say, well, it's not homogeneous there. If you go up into an airplane and look down in your backyard, it's going to look very homogeneous. It's macroscopically homogeneous because you aren't going to be able to see those bare spots.

The point here is, we're talking about many, many granules, like maybe a million. I don't know how many. There's no testimony on how many granules actually are in a tablet, but I think a major dispute here is, are we looking at the whole tablet, or are we looking at a granule or multiple granules within the tablet?

Clearly, our position is you look at, based on how the product is made, in this case, the Zydus case, you look at the granule, the granule. The granules are not a macroscopically homogeneous structure of anything. There are just many, many, many granules throughout this tablet. And when you take a macroscopic picture of this tablet, you'll see all of these granules, and that's what you saw from the Dr. Davies' test. And he picked out specific granules.

Now, the inner lipophilic matrix is within that granule, within the volume of that granule. It's the magnesium stearate. I think it's a question of fact

for this Court as to whether or not you find that it's just magnesium stearate, or it's magnesium stearate and anything else that is in that volume. The only other thing in the volume is mesalamine and the colloidal silicon dioxide.

The testimony we just heard is if, if you find that silicon dioxide is also part of the lipophilic matrix, it's unrelated to the lipophilic characteristic that is created by that inner lipophilic matrix.

Pursuant to, pursuant to the appropriate claim construction --

THE COURT: Hold on, Mr. Haug, and let me just make sure I understand.

MR. HAUG: Yes.

THE COURT: You are saying that the structure is the magnesium stearate on a three-dimensional form captured within, and that if in the agreed-upon definition is a reference to something other than that set of magnesium stearate molecules?

MR. HAUG: No. I think that is the edge. The structure of the magnesium distribution, the three-dimensional magnesium distribution.

THE COURT: Then help me understand what macroscopically means.

MR. HAUG: It means when you are looking --

first of all, we're looking at a pharmaceutical formulation, the whole tablet; right? So the -- the invention here is that you have a dual matrix, two matrices, inner lipophilic and outer; right?

THE COURT: Yes.

MR. HAUG: Macroscopically, if you now go to each granule and you look at the whole tablet, you will find that there's just millions of these granules and the magnesium stearate is throughout. It's uniformly distributed, dispersed throughout the whole formulation, the whole mesalamine formulation. Okay?

And so it's a macroscopically homogeneous distribution that's really -- but it's -- all the granules, you have to look at all of the granules, yes.

THE COURT: All right.

MR. HAUG: That's how we've understood it.

And the question about the inner lipophilic matrix, Mr. Gaertner said the hydrophilic excipient, it can't be an inner lipophilic matrix because is has the hydrophilic excipient, number one.

I think there is a factual question as to whether or not the colloidal silicon dioxide is hydrophilic or not. I think there's one time Mr. Kulkarni said it wasn't. At the end he was shown a corporate brochure and then he said, yes, it is.

And we also have the testimony from Dr. Sinko that says within the context of the patent, it's not hydrophilic, but I think that is a factual finding. However, we also have the testimony that even if, even if it were found to be hydrophilic in any way, it would be unrelated to the lipophilic property, if you will, of the inner lipophilic matrix. I think that goes now to the legal question of consisting of language, which is a whole other legal argument.

And I think there are cases that clearly -- well, actually, the claim construction that we have in this case does exclude excipients which are unrelated to that element.

THE COURT: So what's your testimony relating to outer hydrophilic matrix? What's your evidence?

MR. HAUG: The outer hydrophilic matrix is, again, through the manufacturing process, which goes from the compaction step, which creates the inner lipophilic nature, the granules, the first granules. That then goes to the next step, the wet granulation step, where it is mixed with the sodium starch glycolate, the SSG, and also the sodium CMC, carboxy methylcellulose. Those are both hydrophilic and they are combined, if you will.

They go on top of, was the testimony from Mr. Kulkarni. They go on top of all the granules that are

coming into that wet granulation.

And so you have an inner lipophilic matrix, which is the granule. You then have this outer hydrophilic matrix that also combines with fines that are there in the formulation. And that's the -- you saw the demonstrative that shows the granules going from the compaction step. As they go through the wet granulation step, they become bigger. That's because of the outer hydrophilic matrix that is encapsulating, if you will, or encasing, or on top of, is the testimony of the inner lipophilic matrix.

And then, of course, you have all the evidence of the dissolution of the tablet itself in the photographs that we have from Vivian Gray. And we had that together with the testimony from Dr. Little about the dissolution showing that through those images, that you have an inner lipophilic matrix that creates these granules that, you know, are there, and then they are controlling release of the mesalamine together with the swelling and then the eroding of the hydrophilic, or the outer hydrophilic matrix.

And so that is the key evidence I think, or some of the key evidence about not only the presence of an outer hydrophilic matrix, but also the fact that that outer hydrophilic matrix has hydrophilic properties.

And I think the Hoag test, again, I think it

will be a question of fact for the Court to determine, but the Hoag test was never intended -- it's not a test of the Zydus tablet. It's a test of the simulation of the Zydus tablet specifically looking at comparing the dissolute or the water penetration, if you will, or the rate of penetration of water if you just have mesalamine versus mesalamine with what we said is in the inner lipophilic matrix, the magnesium stearate. And they also included, he also included the colloidal sodium silicon dioxide.

I also believe that there's testimony from Mr. Kulkarni, again, in his 30(b)(6) deposition, where he admitted that they have a hydrophilic matrix on the outside that was -- did not quite say it that way. I don't want to misstate his testimony.

He clearly admitted they have a matrix, and that the matrix is hydrophilic. And, clearly, I think the testimony also that they're separate.

Again, the manufacturing process itself together with the Kulkarni testimony together with the expert testimony of Dr. Little, also by Dr. Sinko, that they do result in separate matrices. I think when you have those elements, inner lipophilic matrix exhibiting lipophilic properties, outer hydrophilic matrix exhibiting hydrophilic properties, and they are separate, that satisfies this Court's claim construction.

On the dispersion issue, whether there's a structure or not is a question of fact. I think on dispersion, clearly, it's -- when we had the claim construction in this case, Zydus argument that, they argued for a claim construction that you have to add mesalamine into each matrix separately, and that was rejected. That was not accepted by the Court. That's not part of the claim construction.

Clearly, when you have mesalamine -- and, again, we have 85 or more percent mesalamine in this formulation. When you add mesalamine and you have it in the inner lipophilic matrix, that then gets -- again, put the outer hydrophilic matrix around it. It is dispersed in both the lipophilic matrix at that point and the outer hydrophilic matrix, plus you have the fines of the mesalamine in the formulation, which also becomes part of the outer hydrophilic matrix.

There's no quantitative requirement in this claim anywhere about how much mesalamine needs to be there at all. And so the whole line of inquiry about how much, you did not quantify how many fines there are, so on and so forth, I don't think are relevant to the -- legally relevant to the question of infringement.

Testing. A lot of, a lot of questions here about the testing that wasn't done not to mention the

testing that was done and trying to critique that. But there's no legal requirement, number one, that we have to test anything to show infringement. It really goes to the, goes to the burden of preponderance of the evidence, and we did do some testing.

I go back to where we were in my opening, which is, the evidence of infringement here, number one, is the Zydus process itself. It's testimony here from Dr. Sinko as well as also from Dr. Little that the manufacturing process alone is sufficient evidence for a finding of infringement. However, in addition to that, we do have testing, some testing. We have pictures that, images that Dr. Davies took, which shows mesalamine everywhere, everywhere in the granules, outside the granules. It's everywhere. It's 80 to 95 percent.

Your Honor asked the question, what's the basis for the percentage, but that's an agreed-upon, undisputed fact in this case. Zydus has agreed that they have more than 80 percent, so it's really not even a disputed question.

And I think that last point also goes to the point I think I heard Mr. Gaertner say about the mesalamine not being mixed. It is mixed. You can see that from the pictures. At least that's a question of fact that Your Honor will have to resolve as to what you do see in those

pictures. But, clearly, the pictures based on how Dr. Davies interprets what is seen as well as Dr. Sinko does show mesalamine being dispersed throughout the formulation, both the inner and the outer.

I think that's it unless Your Honor has anything else.

THE COURT: Thank you very much, Mr. Haug.

Mr. Gaertner, you have the last word.

MR. GAERTNER: A dispersion isn't a structure. I think it's a matter of law it's well within the Court's rights to say that the independent floating particles, that it's admitted by Dr. Sinko, are not connected to one another somehow form a structure on your own. If you were to pull the mesalamine out of that granule that they allege exists and that structure is in there, they would drop to the ground. That's not a structure under any reasonable interpretation of the patent.

And I think as a matter of law there's no question that after hearing that testimony, Your Honor, you can decide that that is not a structure. The patent requires a structure. The matrix must be a structure and it does not satisfy that requirement.

The second item, colloidal silicon dioxide. Dr. Sinko just said it was hydrophilic, and I know we heard a lot about Mr. Kulkarni's confusion in his fact deposition,

but he cleared it up at the end, and we have plaintiffs' own expert conceding that it hydrophilic. But one real point I want to make there is to make sure we're specific. And that is that the consisting of language, it must be unrelated to said element. Said element there is the matrix, not the lipophilic properties of the matrix. It's the matrix itself. And Dr. Sinko just testified that it's hydrophilic colloidal silicon dioxide within the matrix. Okay.

And it's a pore former that increases the amount of water that penetrates into the matrix. So it can't be unrelated to the matrix, and it's certainly not an impurity. Those are the only two limitations that are on that construction of consisting of.

But I want to focus on the structure alone, because I think that is dispositive in terms of the Court's ability to rule as a matter of law that those floating particles, whatever they may be, do not form a structure in which mesalamine is dispersed.

THE COURT: All right. Thank you, Mr. Gaertner.

Well, it's a well argued motion, and in the end there may be aspects of it that ultimately persuade me, but I'm not persuaded at this point, and I will deny it without prejudice.

And we'll begin with your case tomorrow morning. Do you have your witnesses teed up?

MR. GAERTNER: Yes, Your Honor.

THE COURT: All right. Is there anything else we need to talk about this evening before we recess?

MR. GAERTNER: I believe Mr. Peterka needs to move in DTX-8. We'll clean that up tomorrow morning. You don't have to wait.

THE COURT: All right. Do please take a moment to make sure you check on the time distribution and the exhibits all being in. It's good to check that stuff day to day.

And I will look forward to being with you all tomorrow morning, 9:00 o'clock. Thank you very much. And thanks for making allowances for a little bit longer lunch break today. I appreciate it.

(Counsel respond, "Thank you, Your Honor.")

(Court adjourned at 4:58 p.m.)

I hereby certify the foregoing is a true and accurate transcript from my stenographic notes in the proceeding.

/s/ Brian P. Gaffigan
Official Court Reporter
U.S. District Court